Presenter & Disclosure Information

- *Richard Mullvain RPH BCPS(AQC) CCCC*
  - *STEMI Program Manager*
  - *Essentia Health/St. Mary's Medical Center (Duluth, MN)*
  - *Minnesota AHA Mission Lifeline STEMI Project Co-Chair*

FINANCIAL DISCLOSURE:

No relevant financial relationship exists

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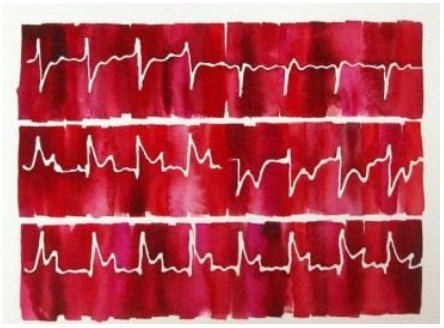
Understanding STEMI Guideline Drugs

…and Pesky Protocol Problems

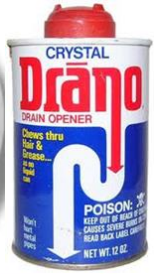


2015 North Dakota State Stroke & STEMI Conference

May 18th – 19th, 2015 – Bismarck, ND

Richard Mullvain, *RPH, BCPS(AQC), CCCC*

- *Clinical Pharmacist*
- *STEMI Program Manager*
- *Minnesota AHA Mission:Lifeline Co-Chair*
- *Essentia Health (Duluth, Minnesota)*



Understanding STEMI Guideline Drugs
…and Pesky Protocol Problems

Objectives & Content:

- Review and apply new knowledge to your practice of the drug recommendations in the most recent 2013 ACC/AHA STEMI Guidelines

- Learn and understand the pharmacology and literature of drugs used in the treatment of ST-Segment Elevation Myocardial Infarction

- Discuss and understand the challenges of following evidence based medicine in STEMI Systems of Care

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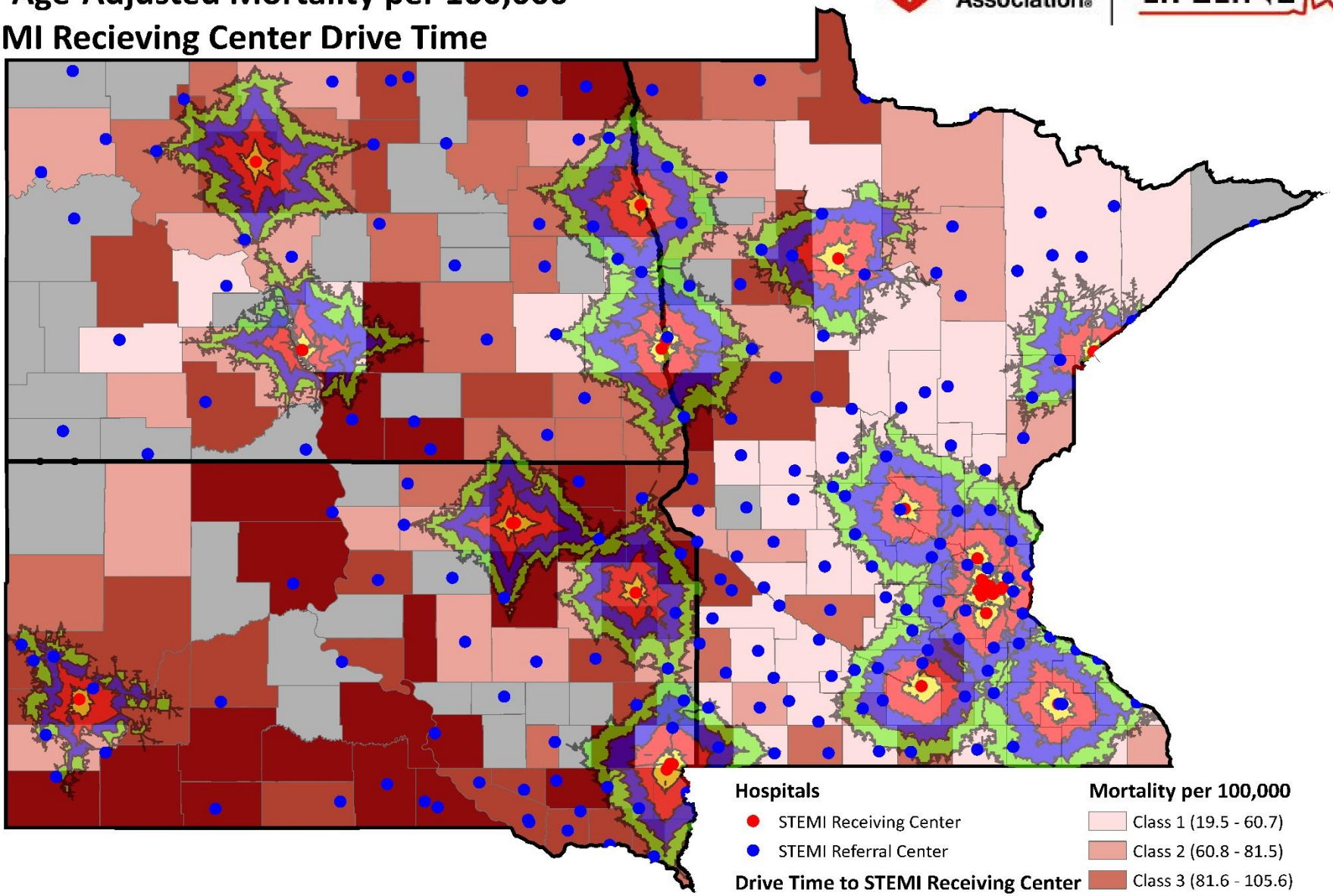
2007-2010 Acute Myocardial Infarction (ICD10 I21 & I22)
35+ Age-Adjusted Mortality per 100,000
STEMI Recieving Center Drive Time

American Heart Association.

MISSION: LIFELINE®

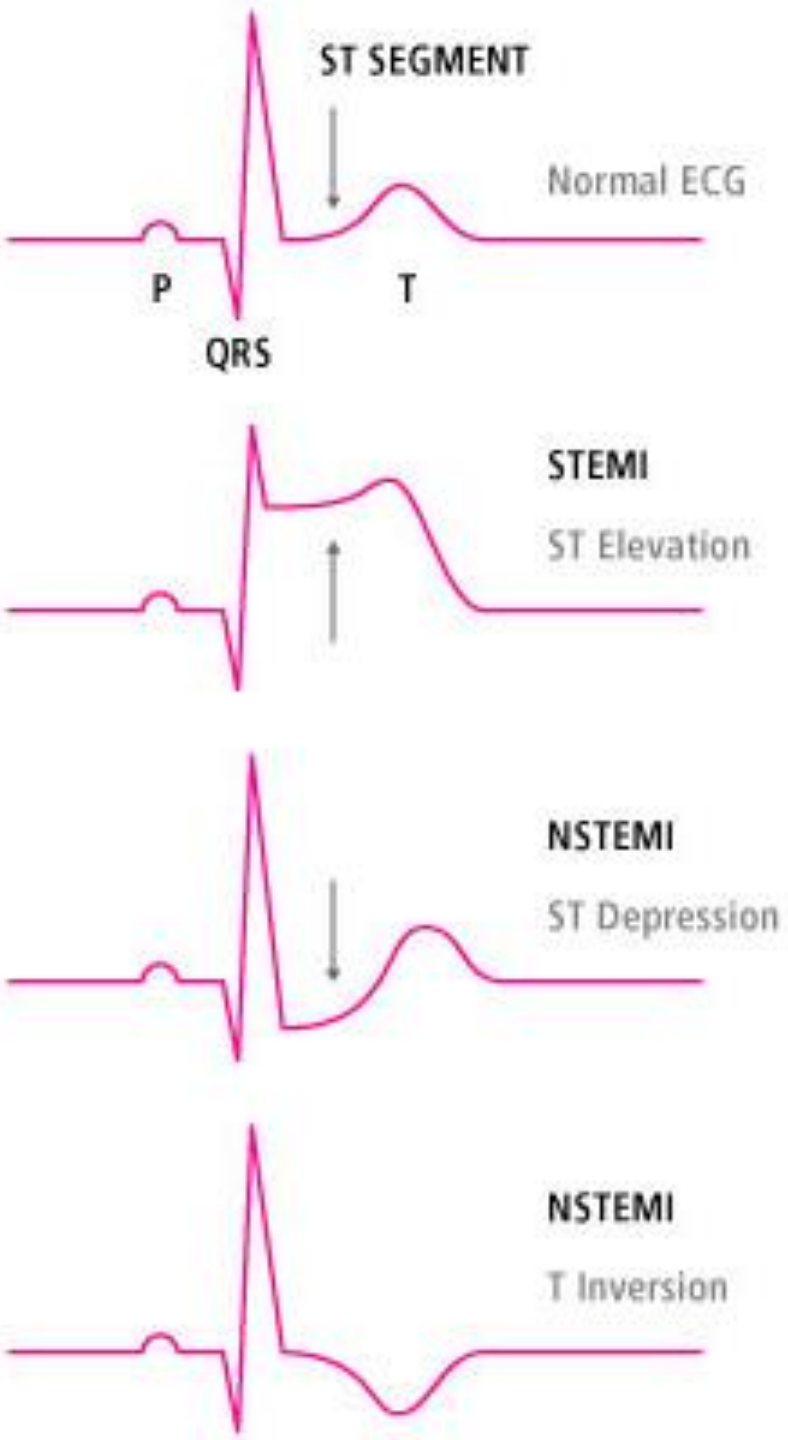


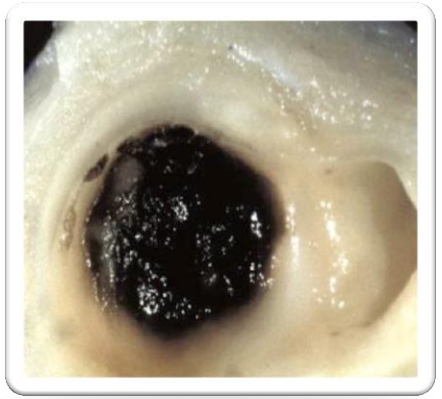
Source: CDC/NCHS Compressed Mortaltiy File 2007-2010.

N

0 25 50 100 150 200 Miles

Created: 4/1/14





Completely blocked artery

Partially blocked artery

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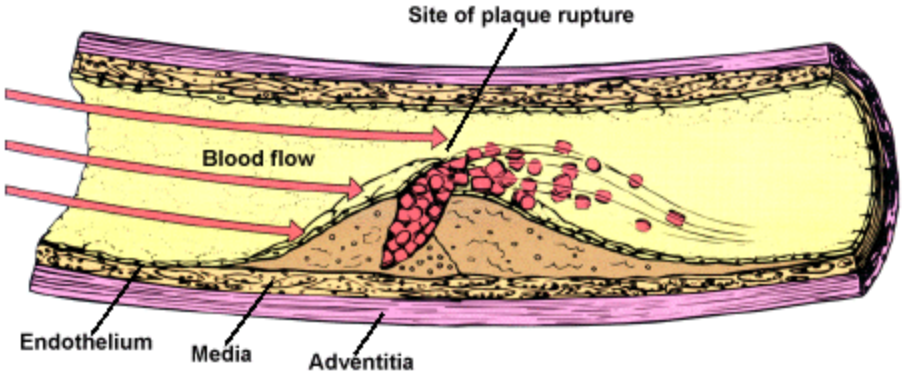
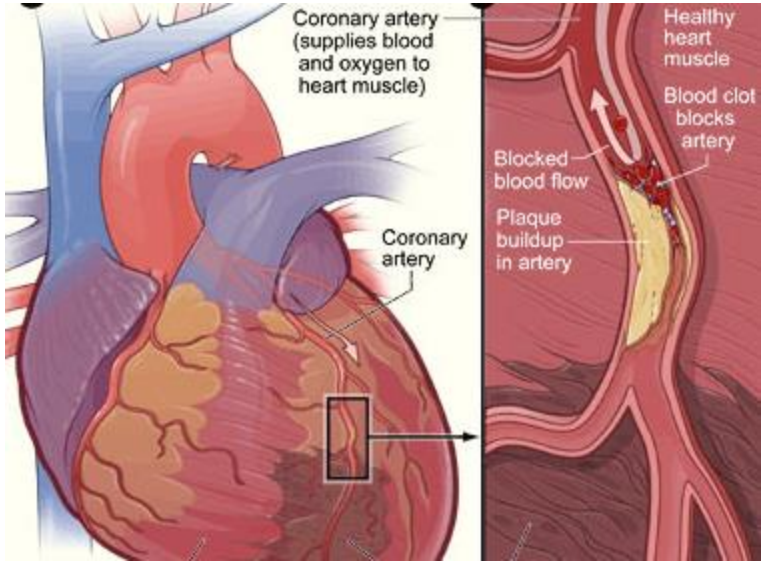
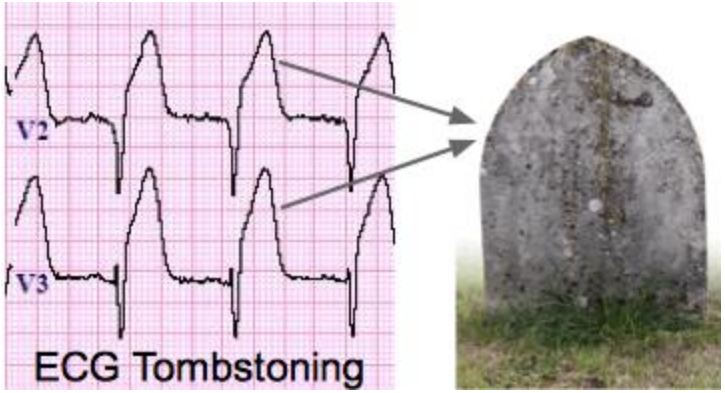
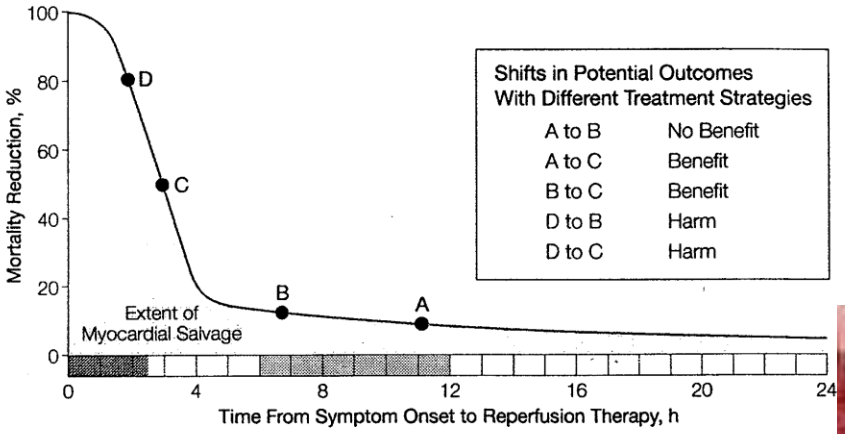

Site of plaque rupture
Blood flow
Endothelium
Media
Adventitia

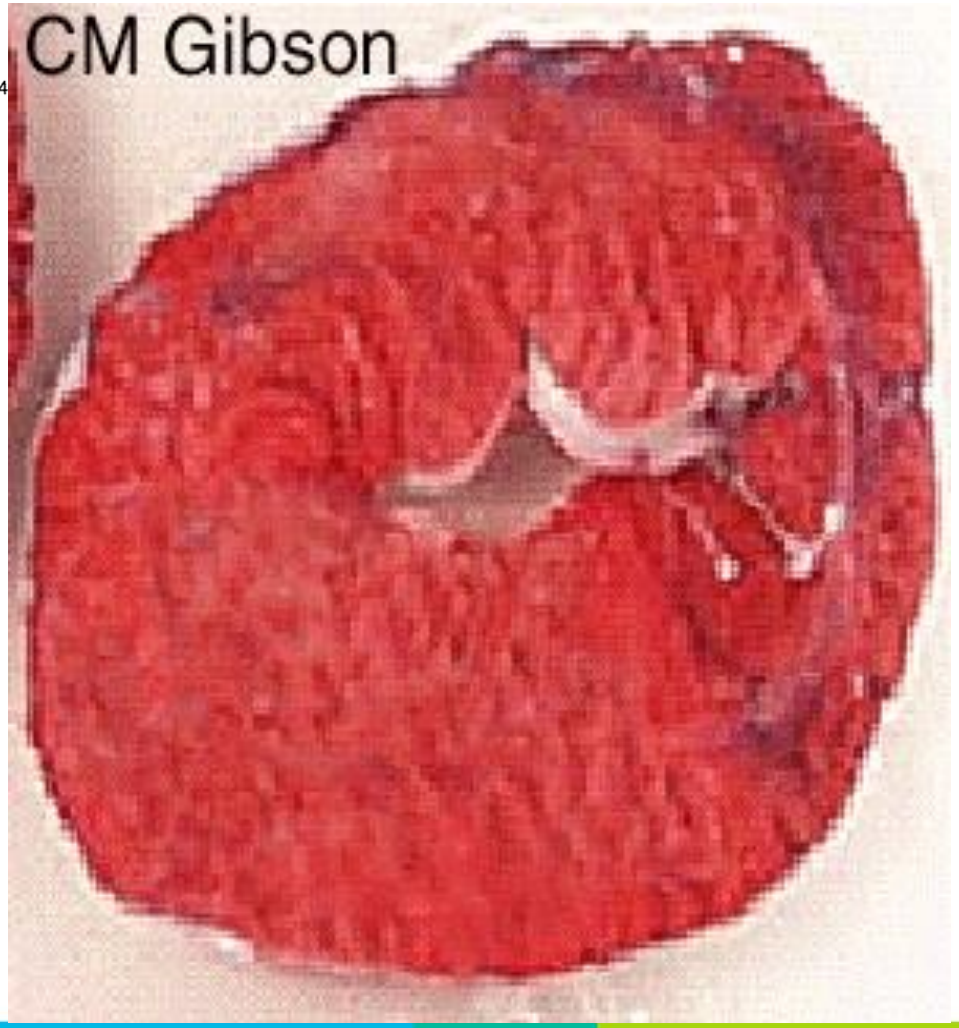

Coronary artery (supplies blood and oxygen to heart muscle)
Healthy heart muscle
Blood clot blocks artery
Blocked blood flow
Plaque buildup in artery
Coronary artery


V2
V3
ECG Tombstoning



Time is Muscle…

“That’s Why We Hustle!”



Gibson CM, Circulation 2001;104:2632-2634

Platelet Aggregation

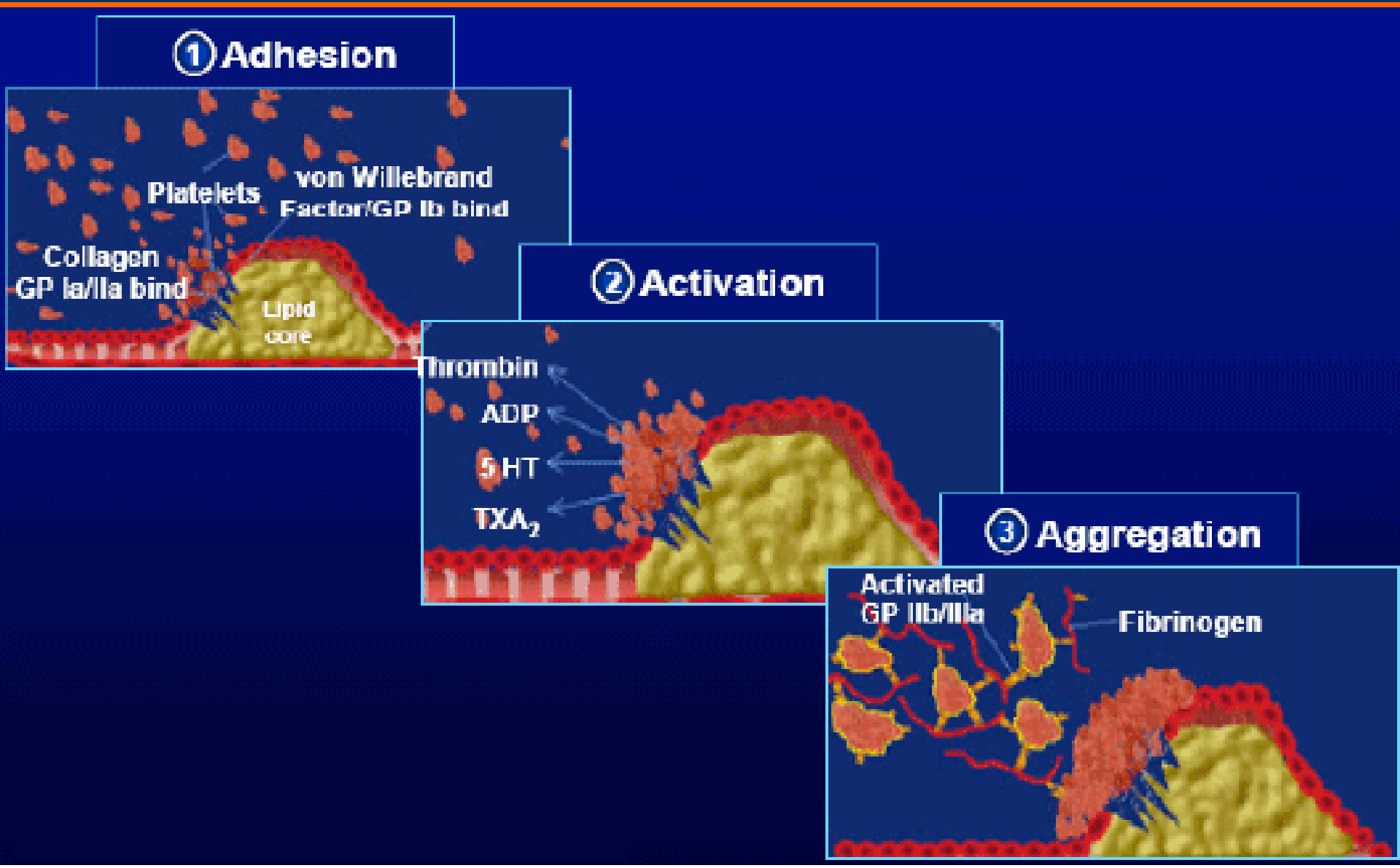
Flowing disc-shaped platelet → Rolling ball-shaped platelet → Hemisphere-shaped platelet → Spreading platelet

FIRM, BUT REVERSIBLE ADHESION

IRREVERSIBLE ADHESION

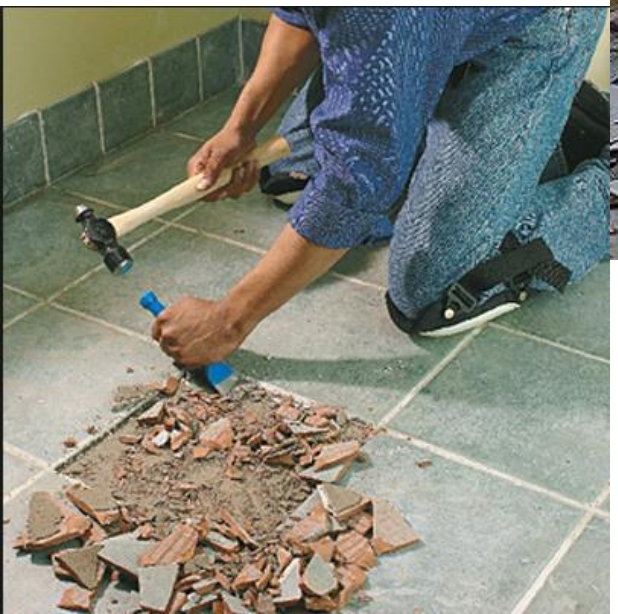
Scanning electron micrograph of discoid, dormant platelets

Activated, aggregating platelets illustrating fibrin strands


1 Adhesion
Platelets
von Willebrand Factor/GP Ib bind
Collagen GP Ia/IIa bind
Lipid core
2 Activation
Thrombin
ADP
5HT
TXA_2
3 Aggregation
Activated GP IIb/IIIa
Fibrinogen

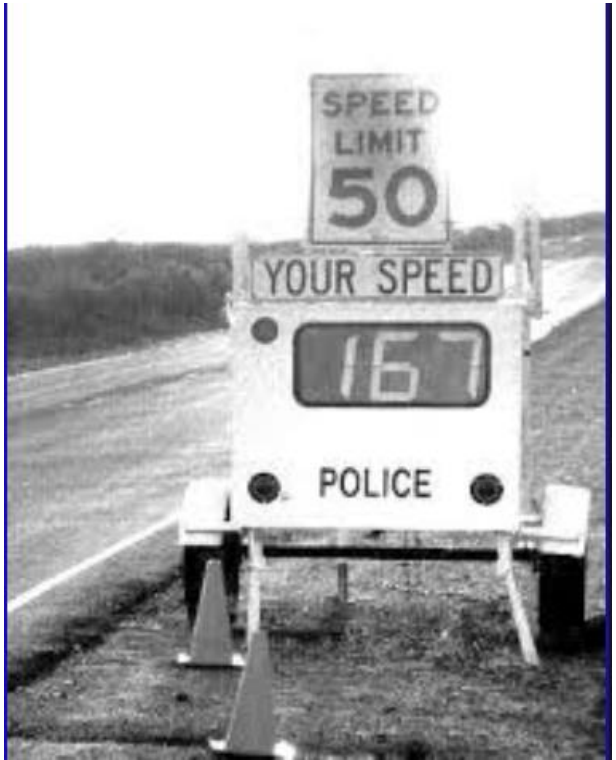
45 yo Male:Pulling Tile,

Then The Chest Pain Started…



Why Call 911?

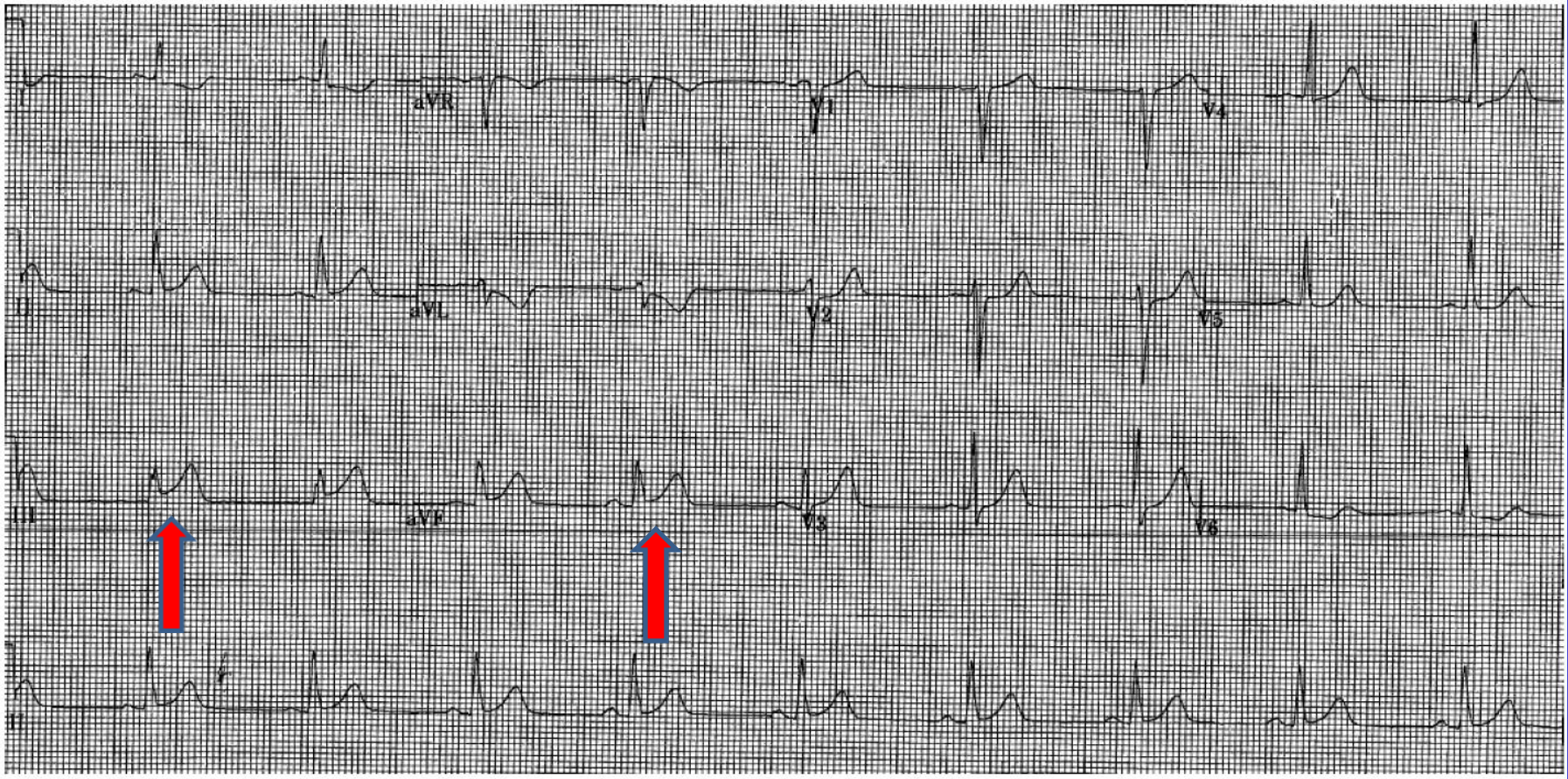
- Wife drove him to Grand Itasca (Grand Rapids, MN) Emergency Department
  - Not sure how fast they went…



45 yo Male w/CP While “Pulling Tile”

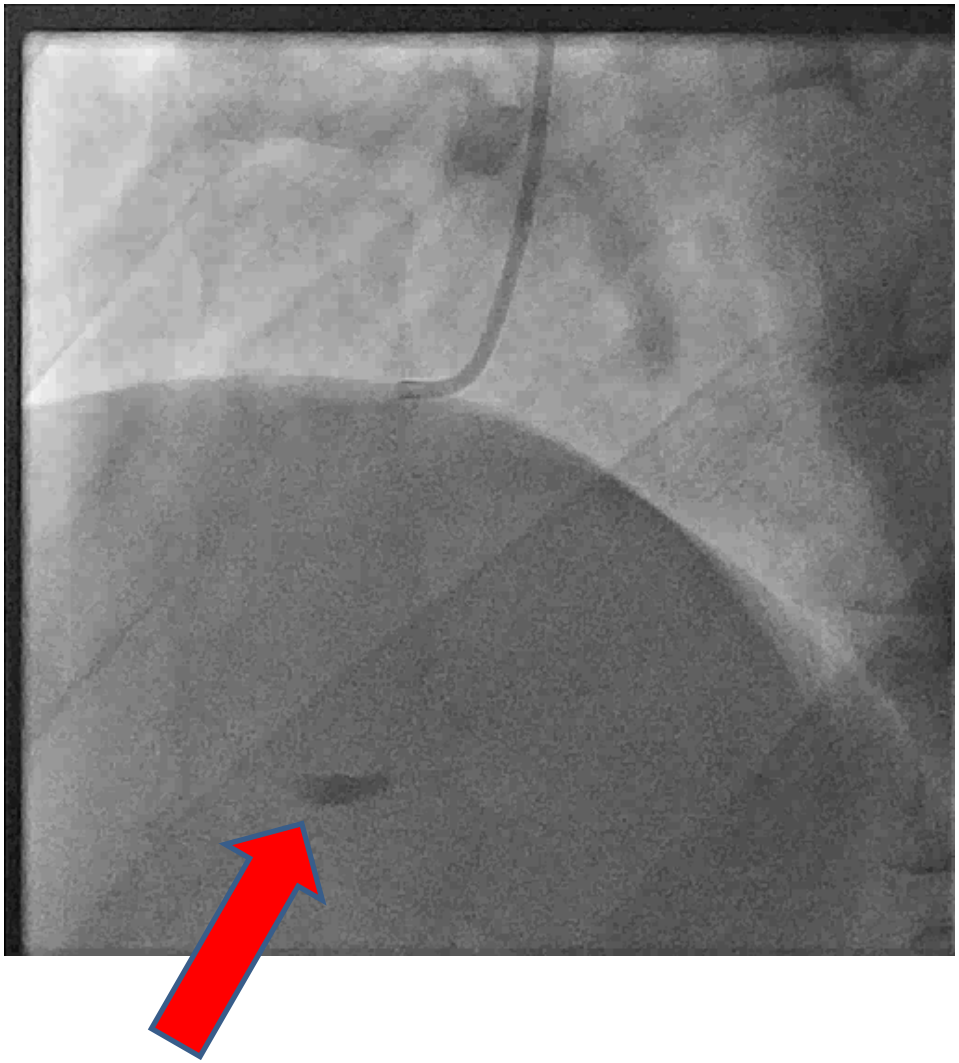
Door to ECG only 4 minutes

12 Lead ECG



45 yo Male w/CP While “Pulling Tile”

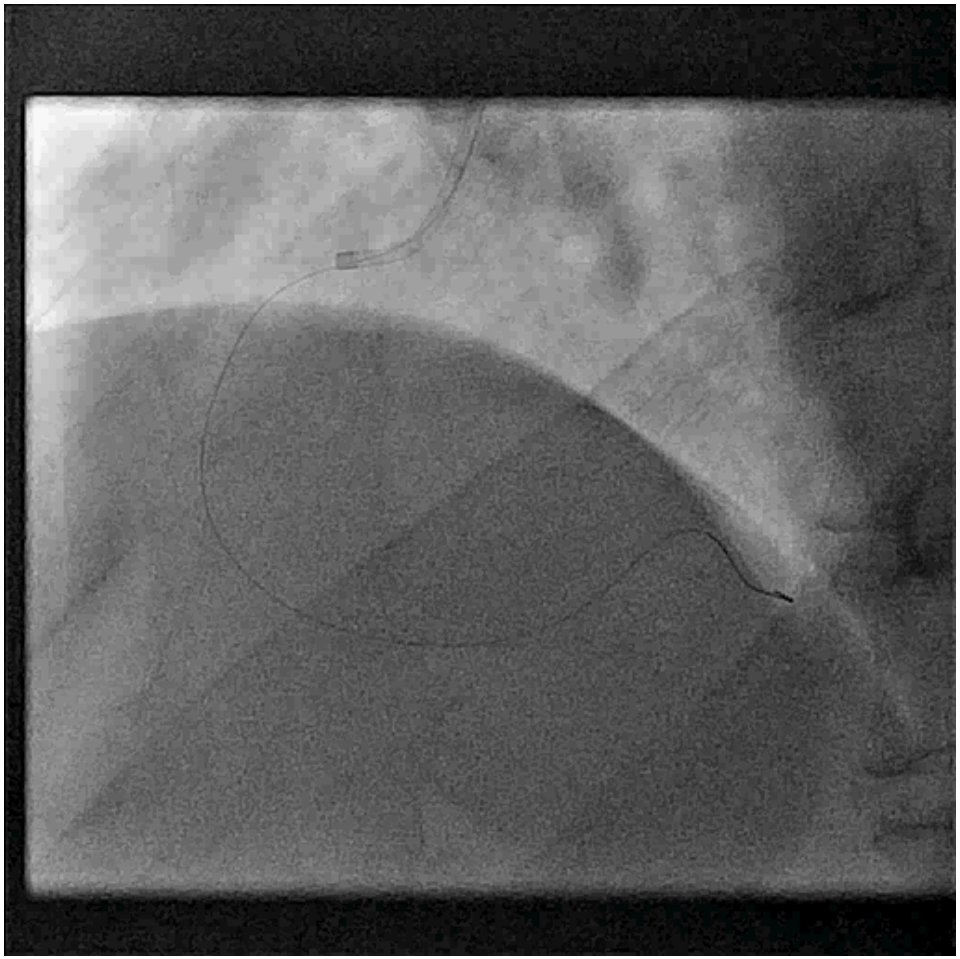
Pre PCI in RCA



What Is That?

45 yo Male w/CP While “Pulling Tile”

Post PCI in RCA



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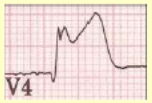
St. Mary's Medical Center



STEMI Feedback Form

Region Hospital

Grand Rapids ED / Life Link III

Date:	Age:	Sex:
11/3/2014	45 year old	Male

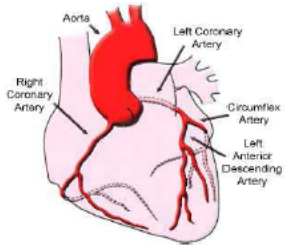
1st Med Contact to Ref.Hosptial to Balloon / Device (Goal ≤ 120 min)	Referral Hospital Door to Balloon / Device (Goal ≤ 90-120 min)	Referral Hospital (+) ECG to Balloon / Device	Referral Hospital Door to ECG (Goal ≤ 10 min)	Call for ALS Transport to Arrive	Patient Door-in -Door-out (DIDO) (Goal ≤ 45 min)	EMS Turnaround (DIDO) (Goal ≤ 10 min)	Transport Time Referral Hospital to SMMC (min)	Essentia SMMC Door to Balloon / Device (min)	SMMC Cath Lab Start to PCI (min)
112	112	108	4	27	59	16	32	21	9

Cath Lab Findings:

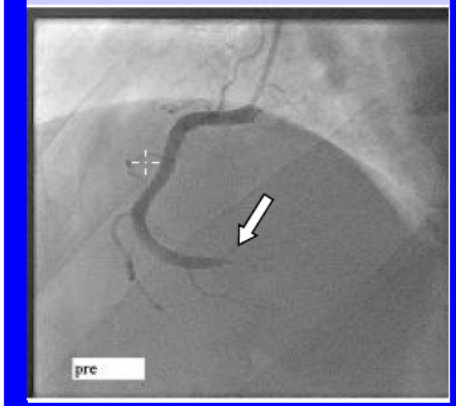
Stent distal RCA

Comments:

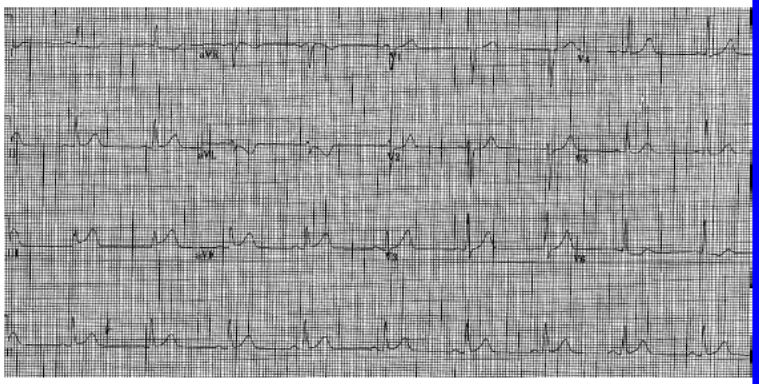
This patient is a 45 year old male who experienced chest pain while pulling tile. He presented to the Grand Itasca ED with wife via private vehicle. There, an ECG was promptly obtained showing Inferior STEMI. Dr. Viren initiated STEMI protocol and the Cath Lab was activated. Life Link III Hibbing, Cory and Eddy, provided air transport, bringing pt directly to the Lab. His distal RCA was found to be totally occluded and was stented with good results. Plan for a staged PCI for mid LAD disease in the future. This patient is very doing well and is recovering on track. Door-to-balloon time of 112 minutes. Terrific! Keep up the good work!



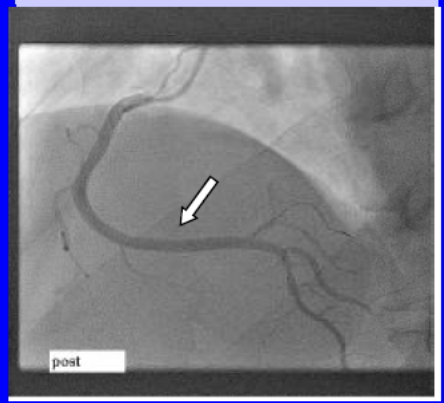
Pre PCI



12 Lead ECG



Post PCI

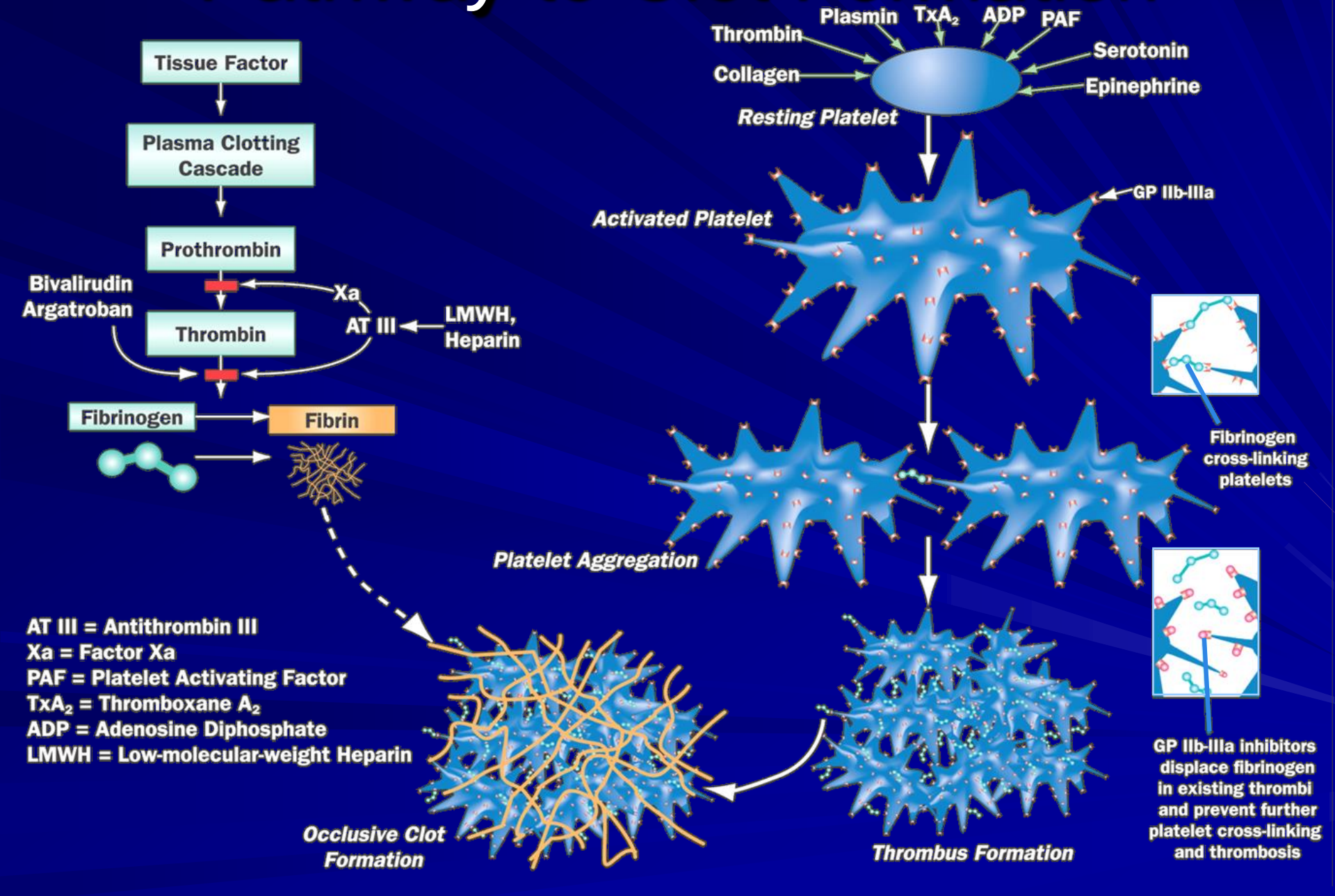


Thank you to all that participated in the care of this patient! Please share this initial feedback with appropriate personnel

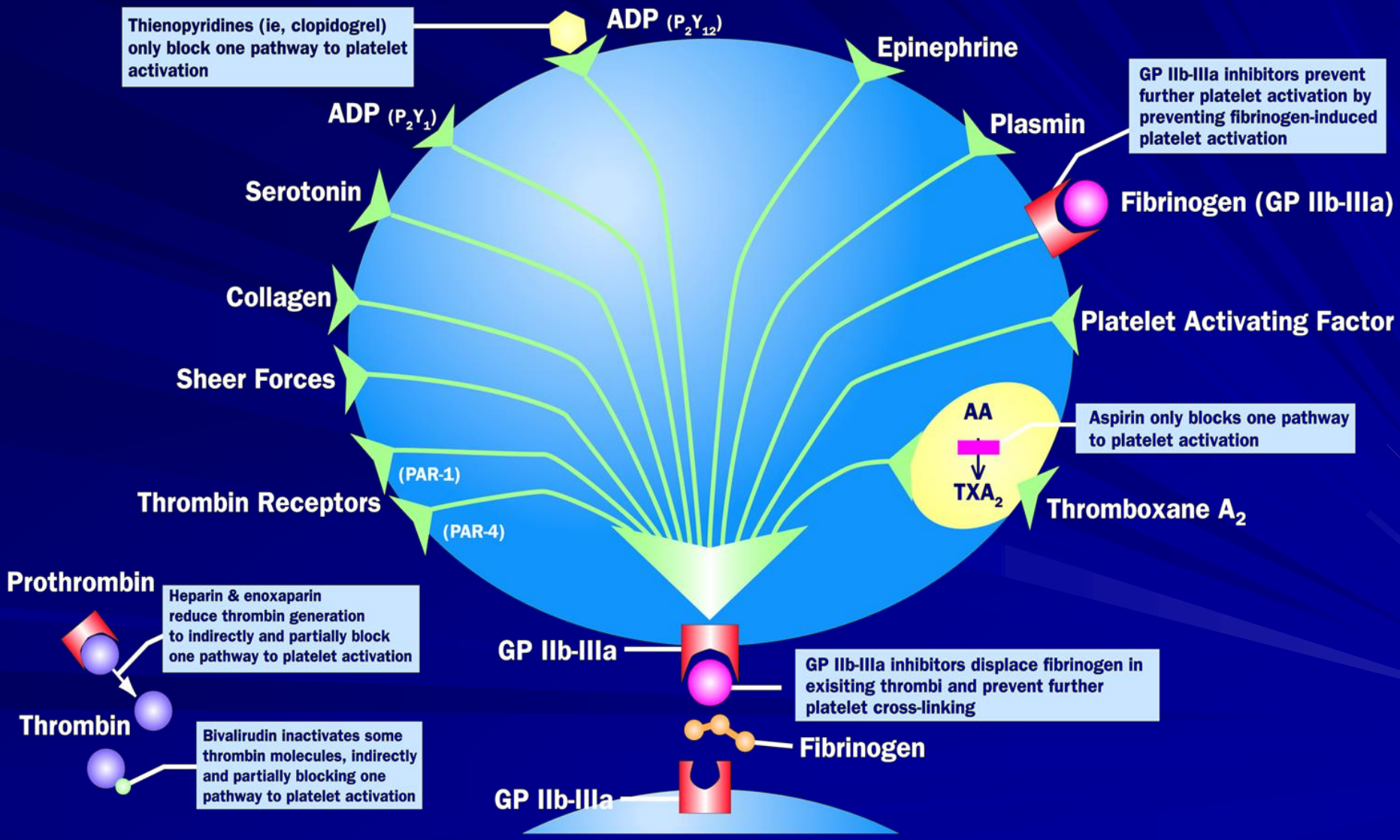
We strive to share accurate and timely feeback to assist with process improvement. If you notice missing or inaccurate data, please notify us.
For any questions or suggestions, contact the Essentia Health / St. Mary's Medical Center STEMI Program Manager:
Richard Mullvain RPH BCPS (AQC) CCCC <> Phone: 218-786-5521 <> E-Mail: richard.mullvain@essentiahealth.org

Essentia Health Mission: *"We are called to make a healthy difference in peoples lives"* **Med Rec #:** 1017996

Pathway to Clot Formation



Pathways to Platelet Aggregation



Not All STEMI's Are The Same!

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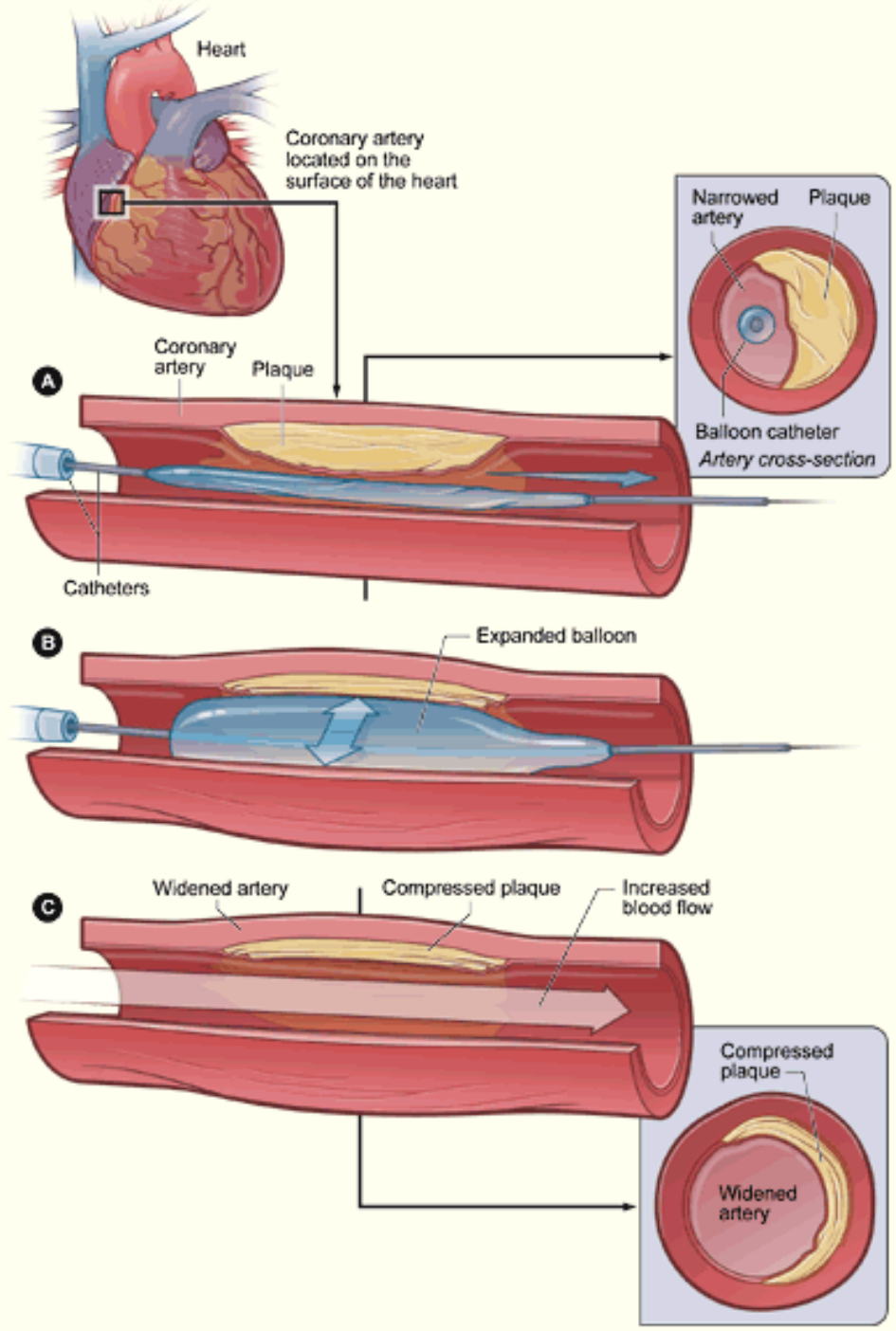
Reperfusion Strategies for STEMI

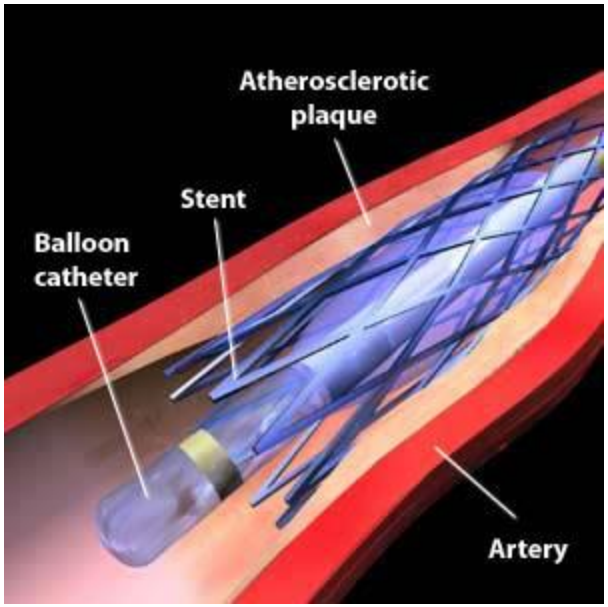
Plan A: percutaneous coronary intervention (primary PCI)

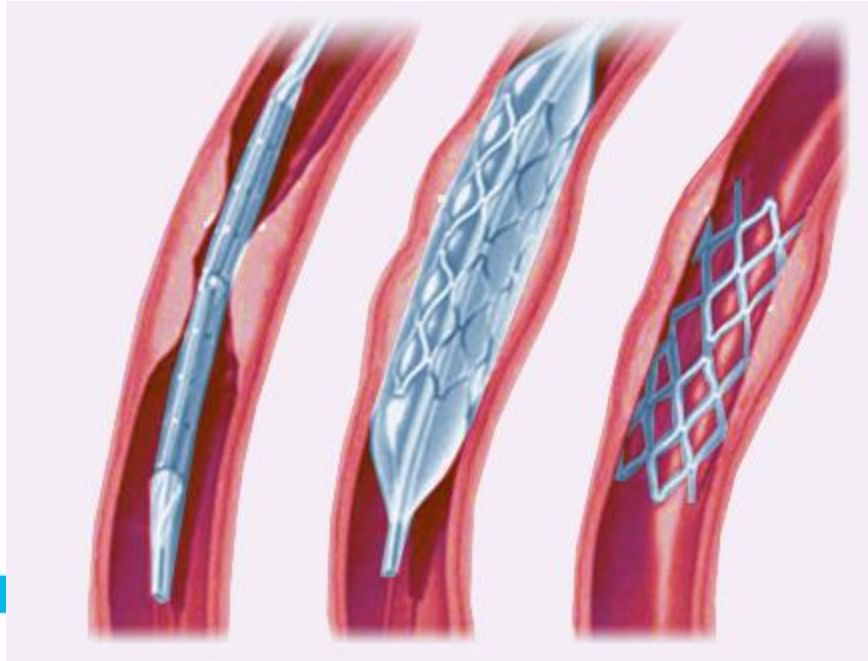
- Mechanical means of restoring blood flow
  - Balloon angioplasty
  - Stents
- More effective
- Lower bleeding risk
- Available at only 25% of U.S. hospitals
  - Treatment delays

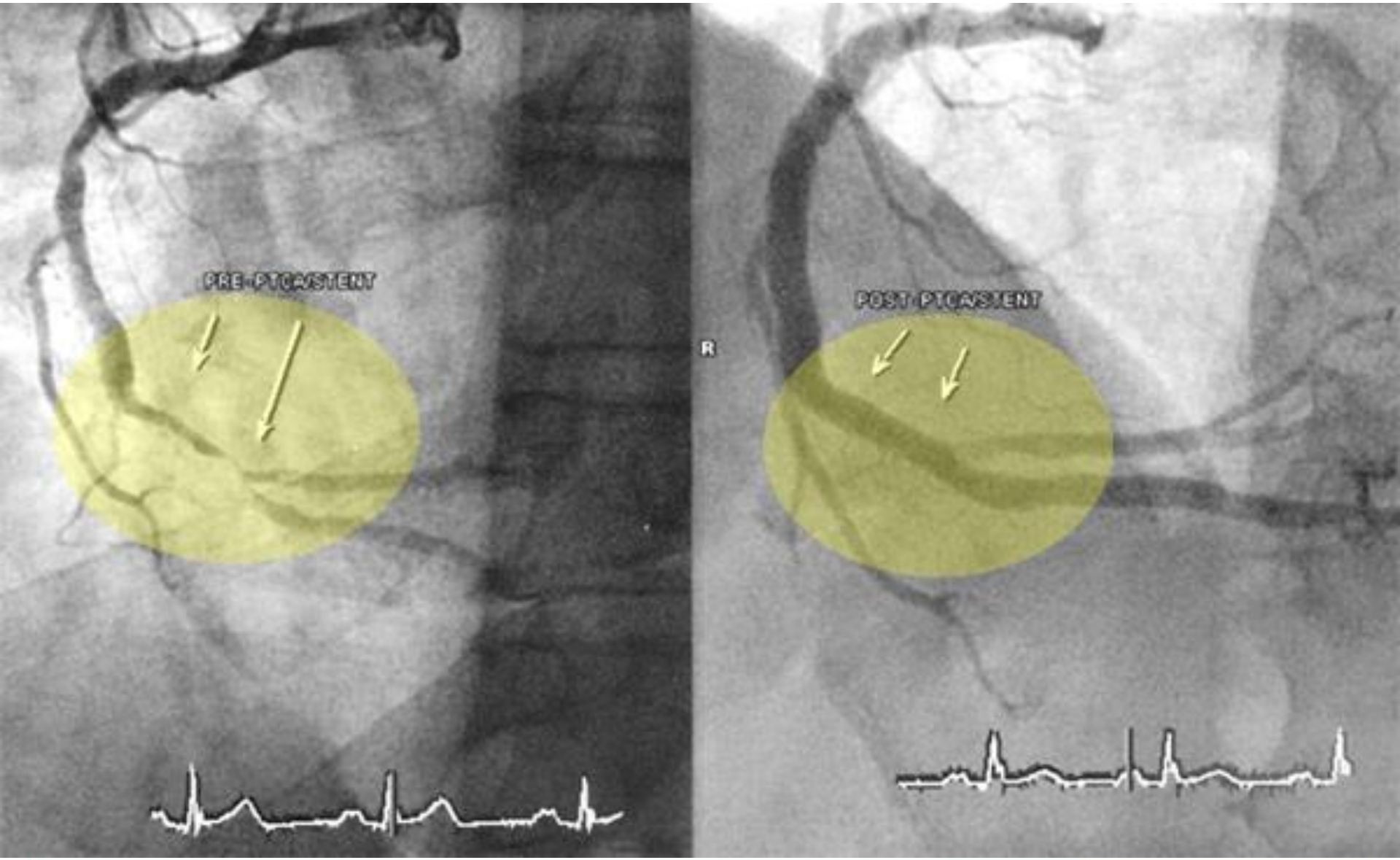
Plan B: thrombolytics (fibrinolytics)

- Pharmacologic means of restoring blood flow
  - "Clot-busting" drugs
- Less effective
- Greater bleeding risk
- Widely available at U.S. hospitals


Heart
Coronary artery located on the surface of the heart
Narrowed artery
Plaque
Balloon catheter
Artery cross-section
A
Coronary artery
Plaque
Catheters
B
Expanded balloon
C
Widened artery
Compressed plaque
Increased blood flow
Compressed plaque
Widened artery


Atherosclerotic plaque
Stent
Balloon catheter
Artery




PRE-PTCA/STENT
R
POST-PTCA/STENT

Blood Thinners….
“What Are They?”

- Anti-Coagulant
- Anti-Platelet
- Anti-Fibrin

Thrombus Remains Following Fibrinolysis

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Van Belle et al. *Circulation.* 1998;97:26-33.

Fibrinolytic Therapy 101

- Lytics can cause serious bleeding!
  - Not indicated for every STEMI!
- Lytics work well if chest pain/symptom onset is within 2-3 hours
- Lytics don’t work as well if symptom onset greater than 4-6 hours

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Is There Only One Answer?

- PCI !!!
- Full Dose Lytic !
- Heparin !
- Angiomax !
- Plavix !

Fibrinolytics !!!

Half-Dose Lytic !

Lovenox !

Heparin?

Brilinta !

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STEMI Drugs

- **Standard**
  - Heparin
  - Aspirin
  - Ticagrelor or Clopidogrel
    - (Brilinta or Plavix)
- **If Appropriate**
  - TNKase
  - Oxygen

- **If Needed (PRN)**
  - Morphine
  - Oxygen
  - Nitroglycerin
  - Diazepam
  - Ondansetron (Zofran)
  - Metoprolol

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We Used to Give Beta Blockers?

CONTRAINDICATION FOR METOPROLOL

Do not give if any of the following: Signs of heart failure or shock, heart rate less than 60 bpm or more than 110 bpm, systolic blood pressure less than 120 mmHg, second or third degree heart block, asthma, or reactive airway disease.

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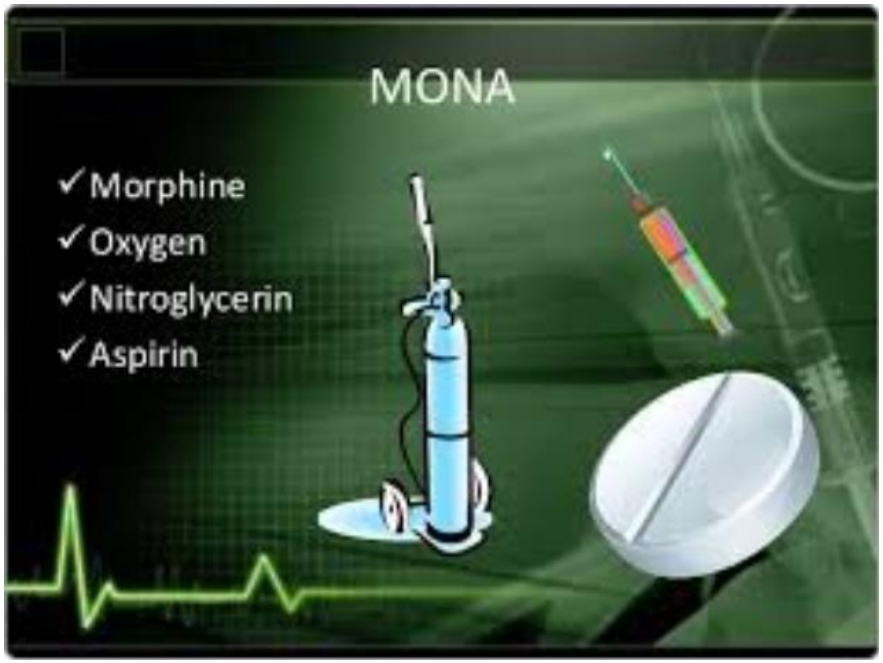
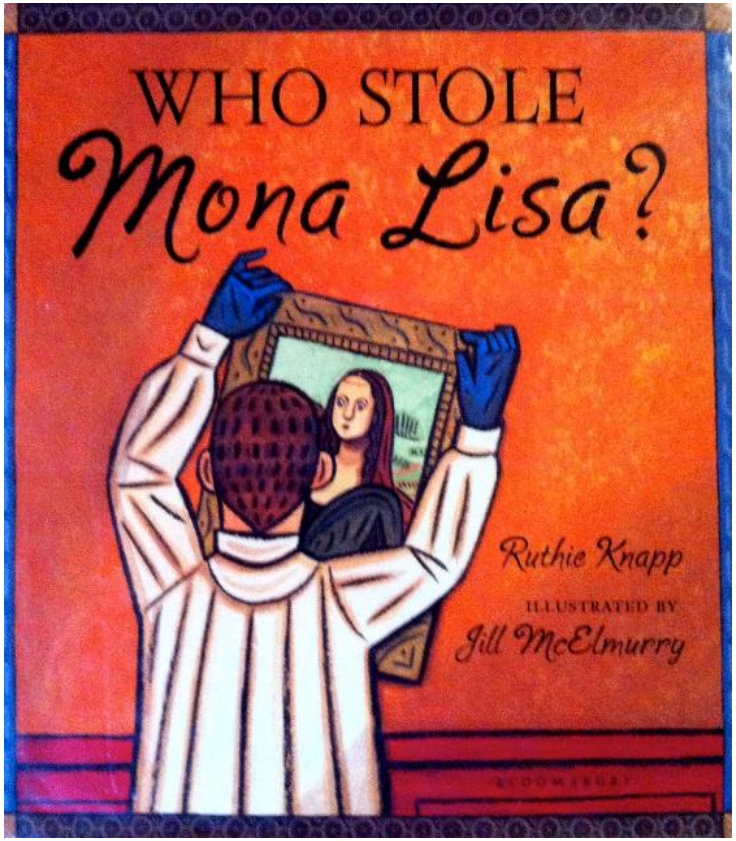
Is MONA Going Away?





Morphine

Oxygen

Oxygen recommendations

Why withhold oxygen in STEMI?

Supplemental oxygen may reduce coronary blood flow, increase coronary vascular resistance and contribute to reperfusion injury through increased formation of reactive oxygen species

Top Patient Care Priorities:

- Establish DNR / Resuscitation Status
- Obtain vital signs and assess pain level on scale of 1-10
- Cardiac Monitor & attach hands-free defibrillator pads
- Establish Saline Lock - large bore needle (left arm preferred)
- Oxygen PRN at 2 L/min and titrate to SpO2 > 90%
- Assess Allergies (Note if reaction to IV Contrast?)

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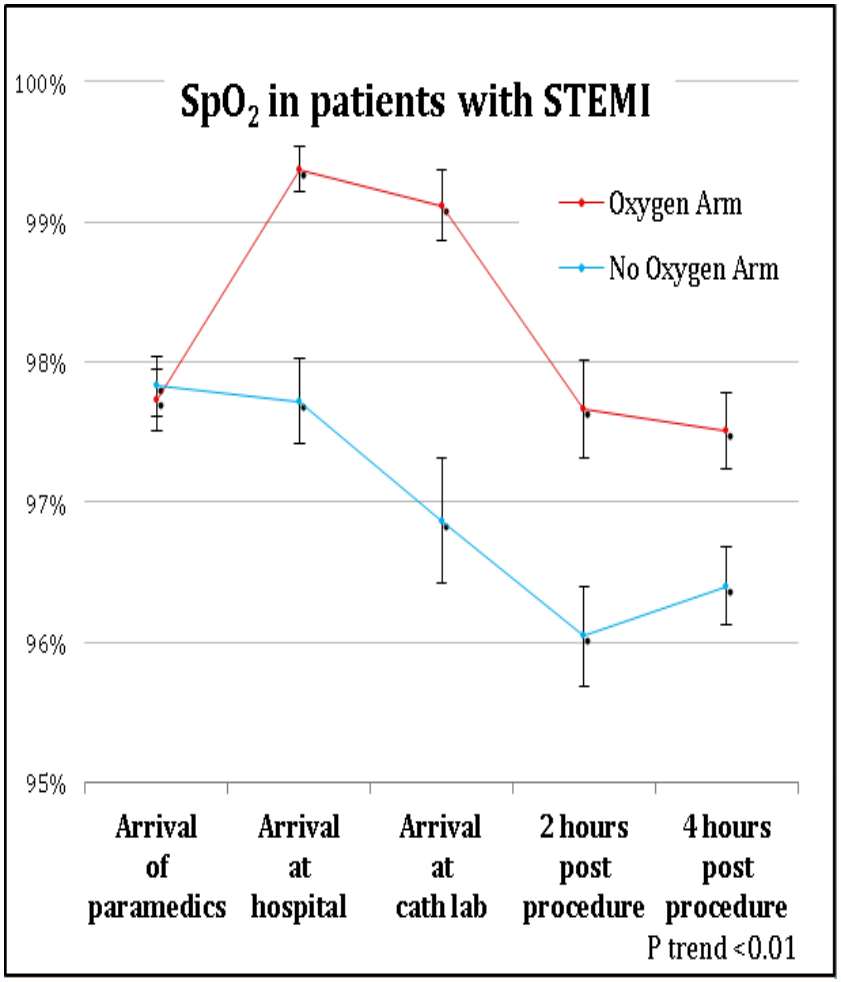
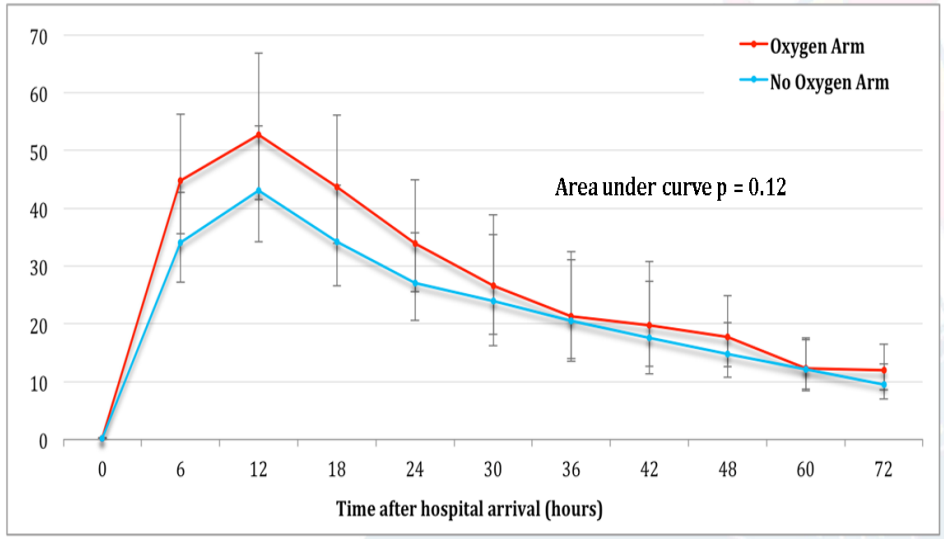
Stub D. A randomized controlled trial of oxygen therapy in acute ST-segment elevation myocardial infarction: the Air Versus Oxygen in Myocardial Infarction (AVOID) study. Presented at: American Heart Association Scientific Sessions; November 19, 2014; Chicago, IL

AVOID (Oxygen in STEMI) Trial



Primary Endpoint Infarct Size

Troponin I, mcg/L	Oxygen Arm N=200	No Oxygen Arm N=205	Ratio of means (Oxygen/No Oxygen)	P-value
Geometric Mean Peak (95% CI)	57.4 (48.0 – 68.6)	48.0 (39.6 – 58.1)	1.20 (0.92 – 1.55)	0.18
Median Peak (IQR)	65.7 (30.1, 145.1)	62.1 (19.2, 144.0)		0.17



www.ambulance.vic.gov.au/research

Stub D. A randomized controlled trial of oxygen therapy in acute ST-segment elevation myocardial infarction: the Air Versus Oxygen in Myocardial Infarction (AVOID) study. Presented at: American Heart Association Scientific Sessions; November 19, 2014; Chicago, IL

AVOID (Air vs Oxygen in STEMI) Trial

Supplemental oxygen therapy in patients with STEMI
but <u>without hypoxia</u> increased..

- Myocardial injury
- Recurrent myocardial infarction
- Major cardiac arrhythmia

… and was associated with **larger** myocardial infarct size assessed at six months

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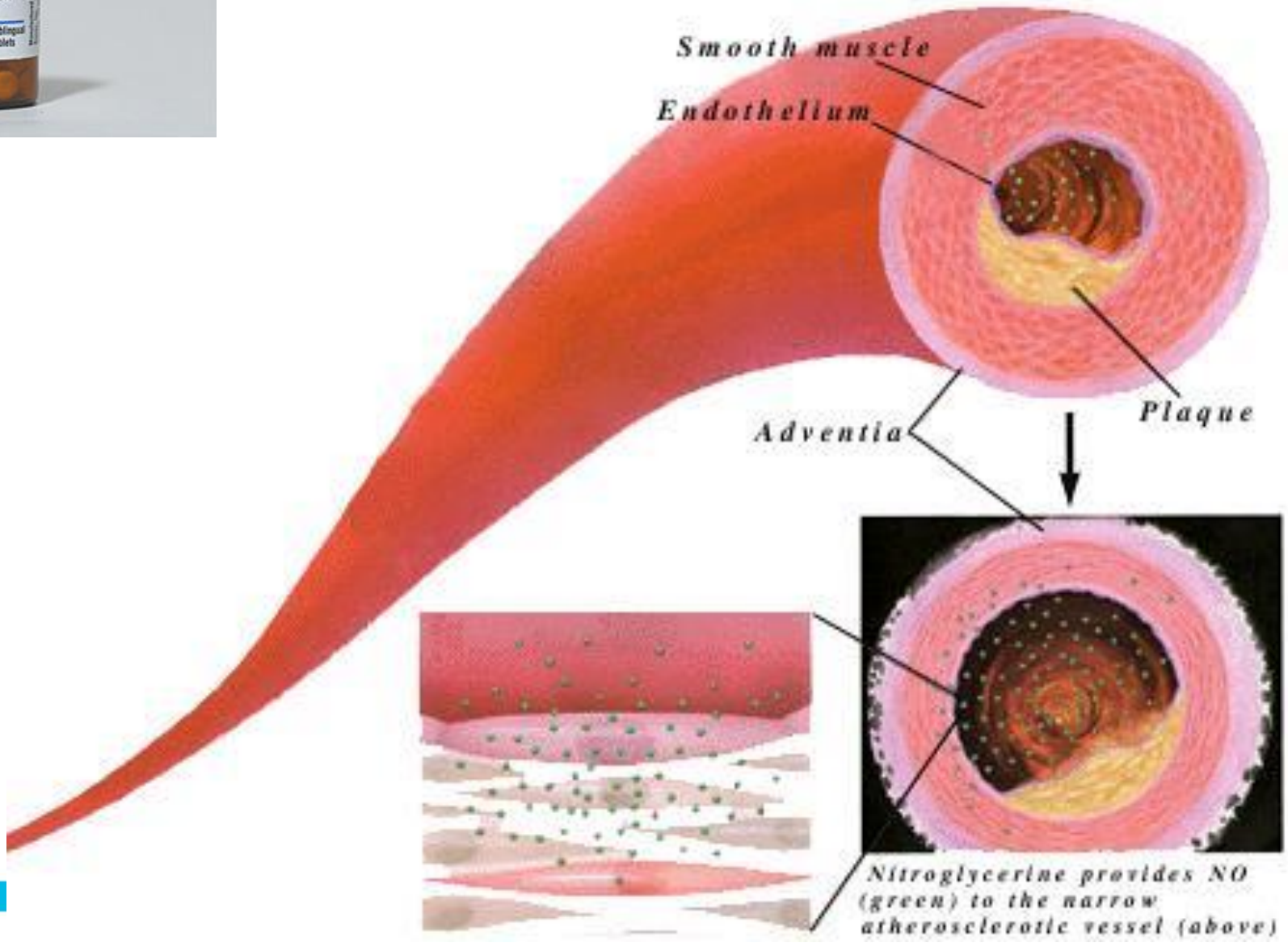
Stub D. A randomized controlled trial of oxygen therapy in acute ST-segment elevation myocardial infarction: the Air Versus Oxygen in Myocardial Infarction (AVOID) study. Presented at: American Heart Association Scientific Sessions; November 19, 2014; Chicago, IL

3

Nitroglycerin



Watch Out For ED or PAH Drugs Before Giving Nitro !

Patient Care When Time Allows:

Establish 2nd large bore IV with Normal Saline @TKO (Left arm preferred)

Obtain Appropriate Labs: Troponin, CBC, Potassium, Creatinine, PT/ INR, aPTT

Nitroglycerin 0.4 mg SL every 5 min or Nitropaste PRN for chest pain (hold for SBP < 90)

Evaluate if erectile dysfunction or pulmonary hypertension medications taken in the past 48 hours including:

Sildenafil (Viagra, Revatio), Vardenafil (Levitra, Staxyn), Avanafil (Stendra), or Tadalafil (Cialis, Adcirca), and if so, hold nitrates for 48 hours

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STEMI Guidelines - 2013

ACCF/AHA Guideline

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions

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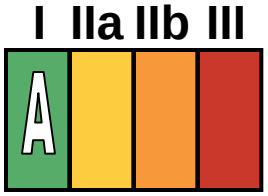
Regional Systems of STEMI Care, Reperfusion Therapy, and Time-to-Treatment Goals

Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the prior 12 hours.

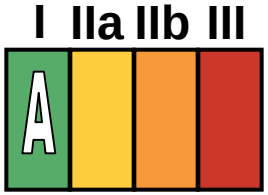


Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators.

EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI with an ideal FMC-to-device time system goal of **90 minutes** or less.*

*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.

Primary PCI in STEMI



Primary PCI should be performed in patients with STEMI and ischemic **symptoms of less than 12 hours**' duration.

Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have **contraindications to fibrinolytic** therapy, irrespective of the time delay from FMC.

Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset.

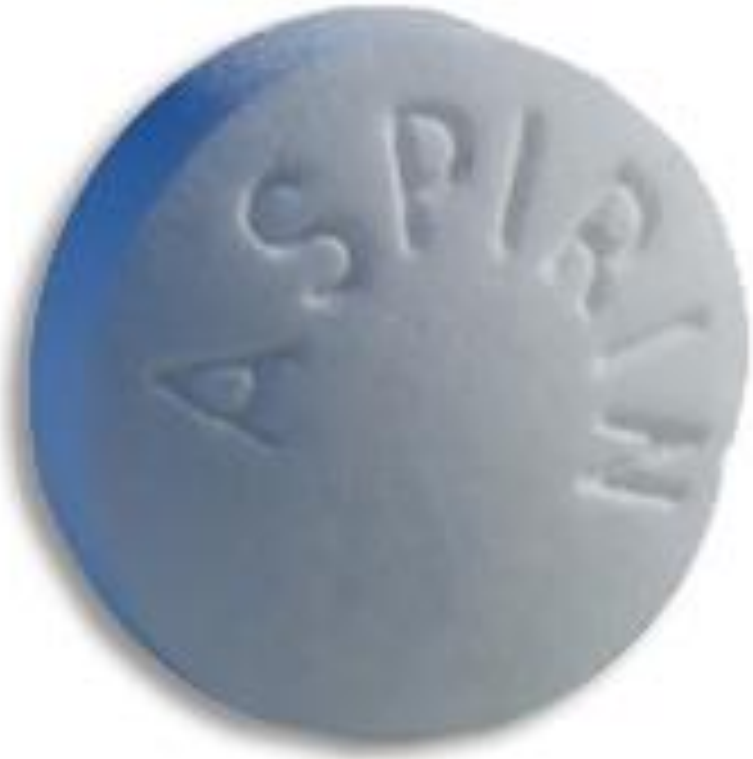
Regional Systems of STEMI Care, Reperfusion Therapy, and Time-to-Treatment Goals

Immediate transfer to a PCI-capable hospital for **primary PCI** is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non–PCI-capable hospital, with an FMC-to-device time system goal of **120 minutes** or less.*

In the absence of contraindications, **fibrinolytic** therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays.

*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.

Aspirin



Antiplatelet Therapy to Support Primary PCI for STEMI

Aspirin 162 to 325 mg should be given before primary PCI.

After PCI, aspirin should be continued indefinitely.

Anticoagulant Therapy to Support Primary PCI

For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended:

- UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered; or

- Bivalirudin with or without prior treatment with UFH.

Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI (cont.)

	COR	LOE
Anticoagulant therapy		
• UFH:	I	C
◦ With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡		
◦ With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT§	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75–mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed.	I	B
◦ Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min		
◦ Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa	B
• Fondaparinux: not recommended as sole anticoagulant for primary PCI	III: Harm	B

‡The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 s.
§ The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 s (HemoTec device) or 300 to 350 s (Hemochron device).

Heparin

…Does the Bolus Dose Matter?

- 4,000 Unit vs. 5,000 Unit I.V. bolus
  - if going to Cath Lab
  - if giving Lytic (TNK)

- IV Drip at 1,000 Units/hr
  - For Lytic patient only?
  - For Long Transports?

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Why Heparin vs. Enoxaparin?

SYNERGY Trial, and other data exists that suggests Enoxaparin (Lovenox) may be better than Heparin

But Enoxaparin is not as practical to use for STEMI, and creates other challenges for patient care

To be given correctly, Enoxaparin must be given as an IV bolus, followed by a Sub-cutaneous injection 15 minutes later

(15 minutes later, we hope a STEMI patient is already on the way to the Cath Lab!)

Subcutaneous absorption can be impacted by a patient in cardiogenic shock, with poor peripheral perfusion

Enoxaparin (Lovenox) comes in pre-filled syringes that cannot be given IV (must transfer to another syringe)

When arriving at the cath lab, we cannot easily measure a bedside anti-Xa to assess level of anticoagulation

If the patient starts to bleed, we cannot easily reverse it with protamine, like we can with Heparin

Heparin is not perfect, but we can easily measure it, reverse it quickly with protamine if need be, and we have the option to switch to Bivailirudin in the cath lab if desired

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Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

Antiplatelet Therapy to Support Primary PCI for STEMI

Harm

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

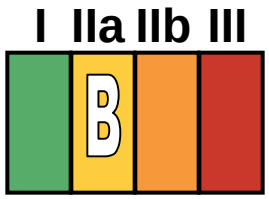
Antiplatelet Therapy to Support Primary PCI for STEMI

$P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

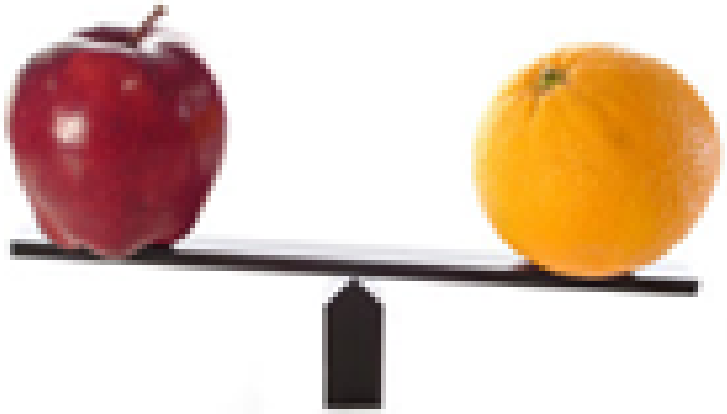
Antiplatelet Therapy to Support Primary PCI for STEMI



It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI.

Ticagrelor or Clopidogrel?

(Brilinta or Plavix?)



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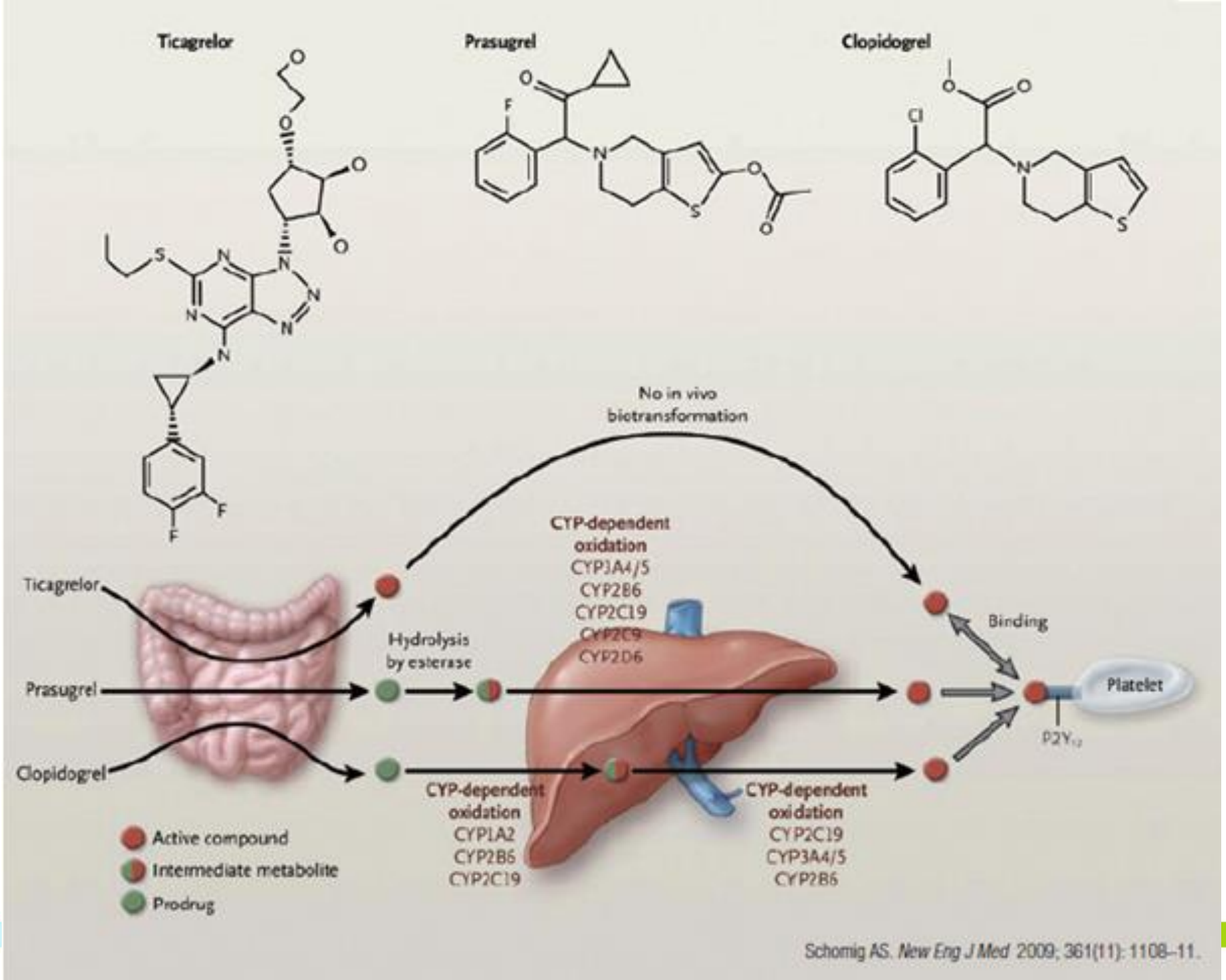


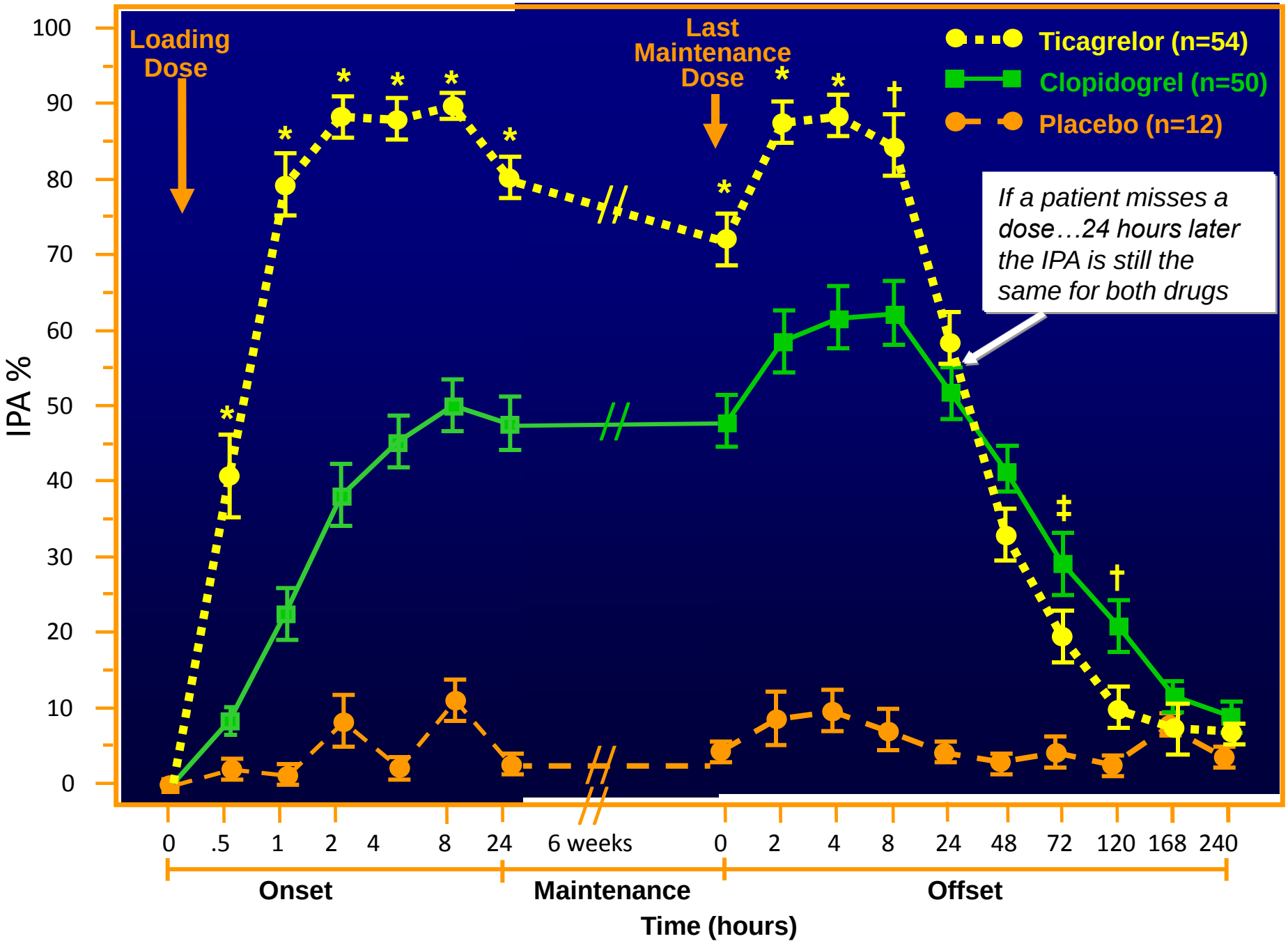
Schomig AS. *New Eng J Med* 2009; 361(11): 1108–11.

How Is Ticagrelor Different?:

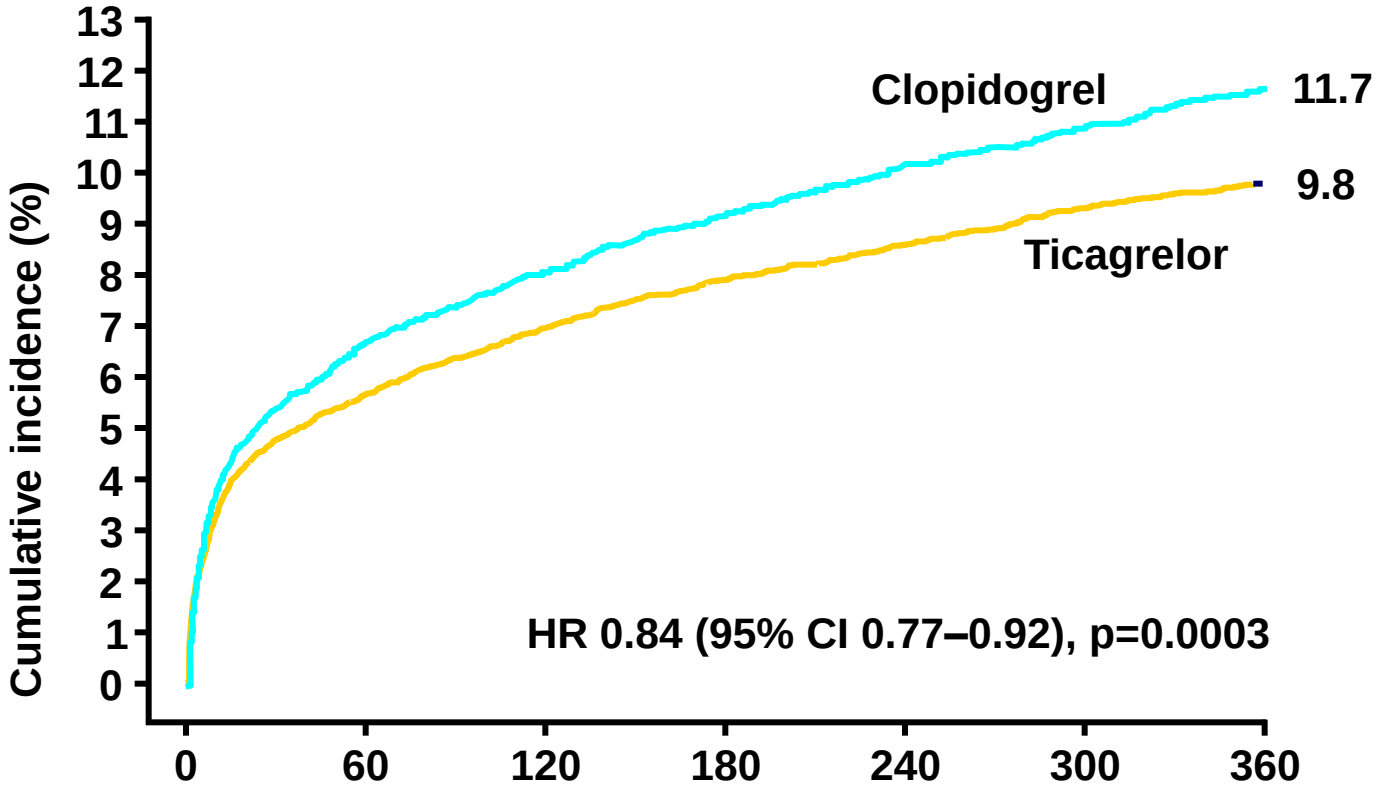
- Not a Pro-Drug
  - Faster platelet inhibition
  - Not subject to genetic variable metabolism
- Adenosine re-uptake may be blocked
  - Vasodilation may reduce ischemia at time of PCI
- Reversible binding to platelets
  - Wears off faster than Clopidogrel or Prasugrel

20 µM ADP- Final Extent

1^0 Endpoint for Onset was met. IPA at 2hrs after first dose(loading): 88% ticagrelor vs. 38% clopidogrel, p<0.0001



K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

PLATO Trial. K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Ticagrelor vs. Clopidogrel or Prasugrel Before Primary PCI – Random Thoughts…

Clopidogrel (Plavix) resistance data is growing, and the FDA issued a Black Box warning highlighting this concern

Prasugrel has more restrictions for those with history of stroke, and limited data for those over 75 years old

Prasugrel has a longer effective half-life, and requires longer washout if bleeding or needing urgent CABG surgery

PLATO Trial demonstrated a mortality benefit of Ticagrelor over Clopidogrel

ATLANTIC Trial did not show Ticagrelor before PCI provided reperfusion, but did reduce stent thrombosis after procedure

Non-STEMI 2014 Guidelines have new language supporting Ticagrelor preferred over the other P2Y12 inhibitors for PCI strategy

On-Set Off-Set Data demonstrates faster and greater platelet inhibition with Ticagrelor vs Clopidogrel

Ticagrelor is not a “Pro-drug”, like Clopidogrel or Prasugrel, which means it is active as soon as it is absorbed from the gut

Clopidogrel and Prasugrel must be metabolized in the liver before actively inhibiting platelets by irreversibly binding to them

Ticagrelor binds reversibly to platelets, and washes out sooner should bleeding occur or surgery be needed

PLATO CABG data suggested that patients can go to surgery sooner after taking Ticagrelor

Ticagrelor triggers an adenosine buildup, leading to coronary vasodilation, which some argue helps explain added benefit

Ticagrelor (Brilinta) is more expensive than generic Clopidogrel (Plavix)

- if necessary, patients can still be switched to Clopidogrel or Prasugrel after starting out on Ticagrelor

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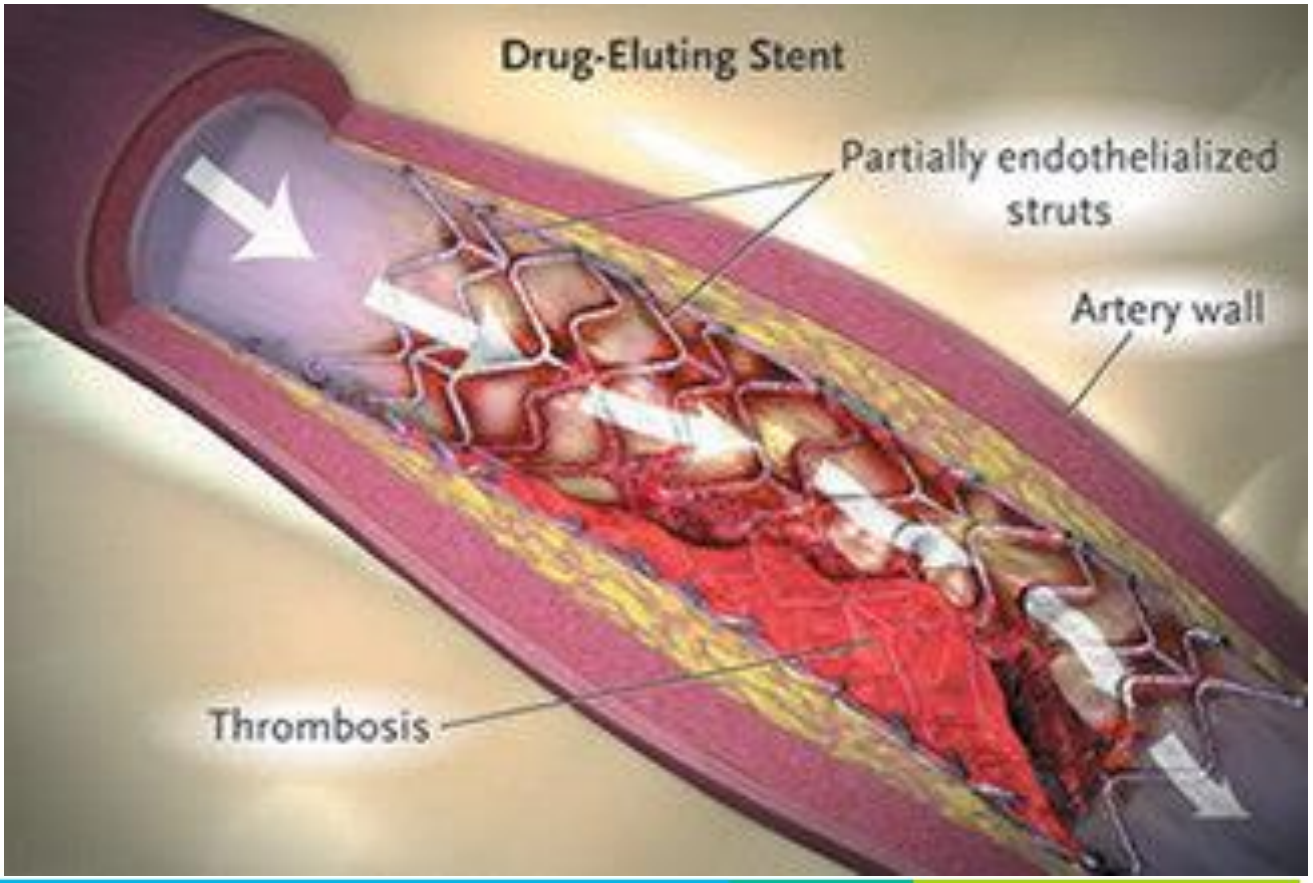
Don’t Stop Plavix, Brilinta, or Effient Before Doctor Tells You!

30 Days for Bare Metal Stent
1 year (Or more?) for Drug Eluting Stent

- Re-Occlusion!



What About STEMI in Europe?

- **European Society of Cardiology** (ESC)
  Updated STEMI Guidelines - August 26th, 2012

EUROPEAN SOCIETY OF CARDIOLOGY

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Steg G, James S, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J 2012; DOI:10.1093/eurheartj/ehs215. Available at: http://eurheartj.oxfordjournals.org/.

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Major gaps in evidence

- Strategies to minimize early cardiac arrest.
- Improving patient and public awareness of STEMI symptoms.
- Optimizing clinical pathways for high-quality, homogeneous early STEMI diagnosis and management.
- Reducing or minimizing myocardial injury and left ventricular dysfunction following STEMI.
- Defining the optimal management strategy for non-culprit vessels in primary PCI patients.
- Defining the optimal long-term antithrombotic regimen in patients receiving stents and who have an indication for oral anticoagulants.
- Defining the role for pre-hospital thrombolysis in patients presenting early.
- Defining the optimal combination and duration of antithrombotic therapies.
- Defining the optimal glucose management goals and strategy in patients with known diabetes or acute hyperglycaemia.
- Developming percutaneous techniques for managing ventricular septal defects.
- Effective and safe of cell therapy to replace myocardium or minimize the consequences of myocardial injury.
- Strategy to minimize risk of sudden death in patients with ventricular tachycardia or ventricular fibrillation during or after STEMI.
- Effective strategies to achieve and maintain long-term effective risk factor control.

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Take home messages

Fibrinolytic therapy

- Fibrinolytic therapy is recommended within 12 hours of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of first medical contact.
- In patients presenting early (<2 hours after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from first medical contact to balloon inflation is >90 min.
- If possible, fibrinolysis should start in the pre-hospital setting.
- A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).
- Oral or i.v. aspirin must be administered. Clopidogrel is indicated in addition to aspirin.
- Anticoagulation is recommended in STEMI patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:
  - Enoxaparin i.v followed by s.c. (preferred over unfractionated heparin),
  - Unfractionated heparin given as a weight adjusted IV bolus and infusion,
  - In patients treated with streptokinase, Fondaparinux i.v. bolus followed by s.c. dose 24 hours later.
- Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients after fibrinolysis.
- Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60 min).
- Emergency PCI is indicated in the case of recurrent ischaemia or evidence of re-occlusion after initial successful fibrinolysis.
- Emergency angiography with a view to revascularization is indicated in heart failure/shock patients after initial fibrinolysis.
- Angiography with a view to revascularization (of the infarct-related artery) is indicated after successful fibrinolysis.
- Optimal timing of angiography for stable patients after successful lysis: 3–24 hours.

Special subsets

- Both genders must be managed in similar fashion.
- A high index of suspicion for MI must be maintained in women, diabetics and elderly patients with atypical symptoms.
- Special attention must be given to proper dosing of antithrombotics in elderly and renal failure patients.

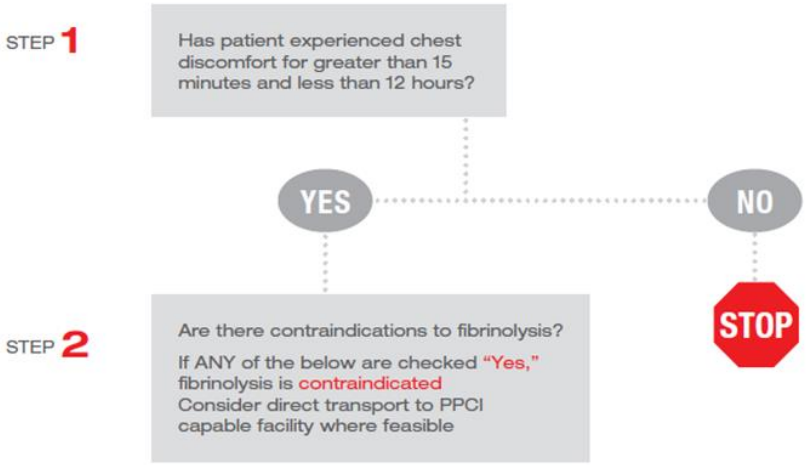
Agency: _____

Patient ID: _____

DOB: _____

American Heart Association. | MISSION: LIFELINE

REPERFUSION CHECKLIST for Evaluation of the Patient with STEMI



YES	NO	ABSOLUTE CONTRAINDICATIONS:	YES	NO	ABSOLUTE CONTRAINDICATIONS:
		Any prior intracerebral hemorrhage			Active bleeding or bleeding diathesis (excluding menses)
		Known structural cerebral vascular lesion (eg, arteriovenous malformation)			Significant closed-head or facial trauma within 3 months
		Known malignant intracranial neoplasm (primary or metastatic)			Intracranial or intraspinal surgery within 2 months
		Ischemic Stroke within 3 months EXCEPT acute ischemic stroke within 4.5 hours			Severe uncontrolled hypertension (unresponsive to emergency therapy)
		Suspected aortic dissection			For streptokinase, prior treatment within the previous 6 months

O'Gara PT, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127

Here's What Minnesota Did with Fibrinolytic Contraindications & Precautions…

ABSOLUTE CONTRAINDICATIONS FOR FIBRINOLYSIS (TNK) IN STEMI

1. Any prior intracranial hemorrhage
2. Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
3. Known malignant intracranial neoplasm (primary or metastatic)
4. Ischemic stroke within 3 months except acute ischemic stroke within 3 hours
5. Suspected aortic dissection
6. Active bleeding or bleeding diathesis (excluding menses)
7. Significant closed-head or facial trauma within 3 months

RELATIVE CONTRAINDICATIONS FOR FIBRINOLYSIS: (TNK) IN STEMI

1. History of chronic, severe, poorly controlled hypertension
2. Severe uncontrolled hypertension on presentation (SBP more than 180 or DBP more than 110 mmHg)
3. History of prior ischemic stroke more than 3 months, dementia, or known intracranial pathology not covered in contraindications
4. Traumatic or prolonged CPR (over 10 minutes)
5. Major surgery (within last 3 weeks)
6. Recent internal bleeding (within last 2-4 weeks)
7. Noncompressible vascular punctures
8. Streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
9. Pregnancy
10. Active peptic ulcer
11. Current use of anticoagulants: the higher the INR ____
12. Symptom Onset > 6 hrs. prior to presentation consult Cardiology

ABSOLUTE CONTRAINDICATIONS FOR FIBRINOLYSIS

- Chest Pain / Symptom Onset > 12 hours
- Suspected aortic dissection
- Any prior intracranial hemorrhage
- Structural cerebral vascular lesion or malignant intracranial neoplasm
- Any active bleeding (excluding menses)
- Ischemic stroke within 3 months
- Significant closed-head or facial trauma within 3 months
- Pregnancy

RELATIVE CONTRAINDICATIONS FOR FIBRINOLYSIS

- Chest Pain / Symptom Onset > 6 hours
- Current use of oral anticoagulants (Warfarin, Dabigatran, Rivaroxaban, Apixaban, etc.)
- Uncontrolled hypertension on presentation (SBP > 180 or DBP > 90 mmHg)
- History of ischemic stroke more than 3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged CPR (over 10 minutes)
- Major surgery within last 3 weeks
- Recent internal bleeding (within last 2-4 weeks)

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Why TNKase vs. RPA or TPA?

Tenecteplase (TNKase) is an effective, fibrin specific clot buster

It can be given as a single 5 second IV bolus, and does not need to be repeated due to it's longer half-life

Reteplase (RPA) is also a reasonable lytic, IV push over 2 minutes, but must be repeated after 30 minutes due to shorter half-life

(We hope STEMI's are on the way to the PCI hospital by then, and second bolus of RPA might get missed)

TPA also works, but is not as practical, and requires 3 steps and 90 minutes to administer

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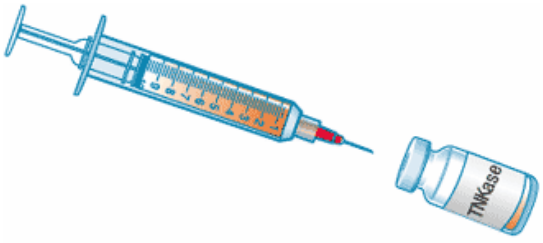

TNKase
(Tenecteplase)

- Door to Needle Goal = 30 minutes
- Contraindications & Precautions
- Full Dose vs. Half-Dose
  - Facilitated PCI
  - Pharmacoinvasive PCI
- Onset of Symptoms
  - Window of time shrinking
    - Less than 3 hours?

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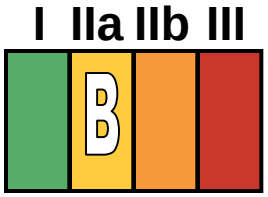
Regional Systems of STEMI Care, Reperfusion Therapy, and Time-to-Treatment Goals

When **fibrinolytic** therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within **30 minutes** of hospital arrival.*

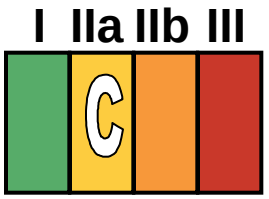


Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of **ongoing ischemia**. Primary PCI is the preferred strategy in this population.

*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.

Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC

In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is **anticipated that primary PCI cannot be performed within 120 minutes** of FMC.



In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability.

Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR.

Adjunctive Antiplatelet Therapy With Fibrinolysis

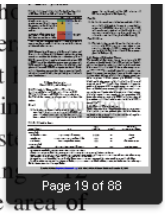
Aspirin (162- to 325-mg loading dose) and clopidogrel (300-mg loading dose for patients ≤75 years of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy.

…Do NOT give Brilinta or Effient with Lytics!

Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy (cont.)

	COR	LOE
Anticoagulant therapy		
• UFH:		
• Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization	I	C
• Enoxaparin:		
• If age <75 y: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses)	I	A
• If age ≥75 y: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first 2 doses)		
• Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h		
• Duration: For the index hospitalization, up to 8 d or until revascularization		
• Fondaparinux:		
• Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization	I	B
• Contraindicated if CrCl <30 mL/min		

What About Half-Dose Lytics?



5. Reperfusion at a Non–PCI-Capable Hospital

5.1. Fibrinolytic Therapy When There Is an Anticipated Delay to Performing Primary PCI Within 120 Minutes of FMC: Recommendations

See Table 4 for a summary of recommendations from this section.

Class I

1. **In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI**

bleeding risk who present within the first 1 to 2 h symptom onset.[123,321] Benefit from fibrinolytic the patients who present >12 hours after symptom onset been established,[81,307,309,322,323] although there remai sensus that consideration should be given to adminis fibrinolytic agent in symptomatic patients presenti hours after symptom onset with STEMI and a large area of myocardium at risk or hemodynamic instability if PCI is unavailable.[4,48]

5.1.2. Choice of Fibrinolytic Agent

Table 5 lists currently available fibrinolytic agents.[314,324–326,328,329] Fibrin-specific agents are preferred when available. Adjunctive antiplatelet and/or anticoagulant therapies are indicated, regardless of the choice of fibrinolytic agent.

Table 5. Fibrinolytic Agents

Fibrinolytic Agent	Dose	Fibrin Specificity*	Antigenic	Patency Rate (90-min TIMI 2 or 3 flow)
Fibrin-specific:				
Tenecteplase (TNK-tPA)	Single IV weight-based bolus†	++++	No	85%[328]
Reteplase (rPA)	10 U+10-U IV boluses given 30 min apart	++	No	84%[314]
Alteplase (tPA)	90-min weight-based infusion‡	++	No	73% to 84%[314,324,326]
Non–fibrin-specific:				
Streptokinase§	1.5 million units IV given over 30–60 min	No	Yes‖	60% to 68%[324,329]

*Strength of fibrin specificity; "++++" is more strong, "++" is less strong.

†30 mg for weight <60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; and 50 mg for ≥90 kg.

‡Bolus 15 mg, infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg.

§Streptokinase is no longer marketed in the United States but is available in other countries.

‖Streptokinase is highly antigenic and absolutely contraindicated within 6 mo of previous exposure because of the potential for serious allergic reaction.

IV indicates intravenous; rPA, reteplase plasminogen activator; TIMI, Thrombolysis In Myocardial Infarction; TNK-tPA, tenecteplase tissue-type plasminogen activator; and tPA, tissue-type plasminogen activator.

…Only "Full" dosing is listed

Half Dose Lytic vs Full Dose Lytic

Two separate issues must be considered when discussing Half-Dose Lytics

1. Pharmaco-Invasive PCI
2. Half-Dose Lytics for those over 75 years old, based on recent STREAM Trial data

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Half Dose Lytic vs Full Dose Lytic: Thoughts On Pharmaco-Invasive PCI

Pharmaco-Invasive PCI remains a controversial issue with some, and trials like ASSENT-4, have suggested worse outcomes

One definition would be the utilization of either half or full dose lytics for all ages, and transfer for urgent PCI as soon as possible

(often within 1-2 hours)

Current Guidelines do not offer good support for this practice, and advise PCI 3 hours or more after successful fibrinolysis

If lytics are not successful (ongoing ischemia, ST resolution < 50%) then rescue PCI is warranted, despite higher bleeding risks

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Half Dose Lytic vs Full Dose Lytic: For those over 75 years old

Half-Dose Lytics for those over 75 years old, based on recent STREAM Trial data

(Note: Previous fibrinolytic trials did not include very many elderly patients)

STREAM was a modern STEMI trial that looked at those that could not get Primary PCI within 1 hour.

After recruiting about 20% of the trial participants, it was noticed that the Intracranial Hemorrhage / Stroke rate for those over 75 years old was over 8%.

The STREAM Trial changed their protocol to give Half-Dose lytics to those over 75 years old, and after that, there were no more strokes reported in that age group, and outcomes remained good.

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Armstrong, et al; Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction (STREAM Investigation Team);NEJM, March 10th, 2013.

Table 3. Strokes and Nonintracranial Bleeding Events within 30 Days.

Event	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value
	no./total no. (%)		
Total strokes	15/939 (1.6)	5/946 (0.5)	0.03
Intracranial hemorrhage			
Any	9/939 (1.0)	2/946 (0.2)	0.04
After protocol amendment*	4/747 (0.5)	2/758 (0.3)	0.45
Primary ischemic stroke			
Without hemorrhagic conversion	5/939 (0.5)	3/946 (0.3)	0.51
With hemorrhagic conversion	1/939 (0.1)	0/946	0.50
Nonintracranial bleeding			
Major	61/939 (6.5)	45/944 (4.8)	0.11
Minor	205/939 (21.8)	191/944 (20.2)	0.40
Blood transfusion	27/937 (2.9)	22/943 (2.3)	0.47

* On August 24, 2009, the study protocol was amended to reduce the dose of tenecteplase by 50% in patients 75 years of age or older because of an excess of intracranial hemorrhage in this age group.

Rates of stroke were low in the two study groups, but both intracranial hemorrhagic and primary ischemic strokes were more frequent in the fibrinolysis group than in the primary PCI group (Table 3). After the dose reduction of tenecteplase in patients 75 years of age or older, there were no cases of intracranial hemorrhage (0 of 97 patients), as compared with 3 of 37 patients (8.1%) in this age group before the amendment. The rate of major nonintracranial bleeding was 6.5% in the fibrinolysis group, and 4.8% in the primary PCI group, a difference that was not significant (P=0.11). The rates of blood transfusions were also similar in the two study groups (2.9% and 2.3%, respectively; P=0.47).

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Armstrong, et al; Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction (STREAM Investigation Team);NEJM, March 10th, 2013.

STREAM Trial Findings...

A strategy of fibrinolysis with bolus tenecteplase and contemporary antithrombotic therapy given before transport to a PCI-capable hospital coupled with timely coronary angiography :

- Is as effective as primary PCI in STEMI patients presenting within 3 hours of symptom onset who cannot undergo primary PCI within one hour of first medical contact
- Circumvents the need for an urgent procedure in about two thirds of fibrinolytic treated STEMI patients
- Is associated with a small increased risk of intracranial bleeding
- *(Demonstrated safety and effectiveness of half-dose TNK for those over 75 years old)*

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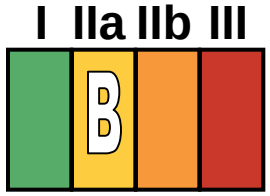
Armstrong, et al; Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction (STREAM Investigation Team);NEJM, March 10th, 2013.

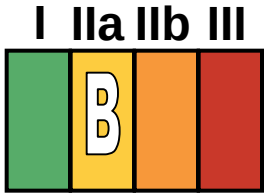
Transfer of Patients With STEMI to a PCI-Capable Hospital for Coronary Angiography After Fibrinolytic Therapy

Immediate transfer to a PCI-capable hospital for coronary angiography is recommended for suitable patients with STEMI who develop cardiogenic shock or acute severe HF, irrespective of the time delay from MI onset.

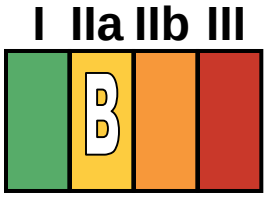


Urgent transfer to a PCI-capable hospital for coronary angiography is reasonable for patients with STEMI who demonstrate evidence of failed reperfusion or reocclusion after fibrinolytic therapy.

Coronary Angiography in Patients Who Initially Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion



Coronary angiography with intent to perform revascularization is reasonable for patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy. Angiography can be performed **as soon as logistically feasible**.



Coronary angiography is reasonable before hospital discharge in stable* patients with STEMI after successful fibrinolytic therapy. Angiography can be performed as soon as logistically feasible, and ideally within 24 hours, but should not be performed within the first **2 to 3 hours after administration of fibrinolytic** therapy.

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

Yes, it is a STEMI…But please don't drive too fast!

END OF PRESENTATION

QUESTIONS?

THANK YOU!

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